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POSTHERPETIC TRIGEMINAL NEURALGIA

OSCAR SUGAR, M.D.
AND
PAUL C. BUCY, M.D.
CHICAGO

THE PAIN which may follow herpes zoster may be so severe as to lead to suicide (Forget[1]). William Bowman[2] wrote (1867): "I wish I could state anything very satisfactory as to the treatment of the after-pains, which are sometimes so severe as to make the patient weary of existence." In 1901 Mules[3] reported a case in which the pains were so violent that the patient applied carriage varnish and liniment to the scalp; this caused severe dermatitis and eventual sloughing of the skin of the forehead down to the pericranium. When the man recovered, his pain had disappeared.

It is common for pain to precede the outbreak of the vesicles which appear at the terminal ramifications of the sensory nerves in herpes zoster. It is usual for the pain to disappear at this time, or to linger on during the course of the eruption for a while, to disappear with the healing of the skin. In some patients the pain persists for months or years. Trousseau[4] described two cases in which the pain persisted five and 14 years after the eruptions, and Rea[5] mentioned a patient with pain for at least six years after the lesions of the skin. The pain is tenacious and persistent and has a detrimental effect on the general state of health of the patient. It is particularly distressing when it follows herpes zoster of the fifth cranial nerve; any branch of this nerve may be involved, but by far the most commonly affected division is the ophthalmic. Postherpetic trigeminal neuralgia is usually found beyond the age of 40, and slightly oftener in men than in women (Edgerton[6]). According to Head,[7] trigeminal zoster is next commonest after thoracic involvement.

From the Department of Neurology and Neurological Surgery, University of Illinois, Illinois Neuropsychiatric Institute.

1. Forget: Du zona et de son traitement: notamment par les vésicatoires, Bull. gén. de thérap. **61**:337-340, 1861.

2. Bowman, W.: Cases of Zoster, or Unilateral Confluent Herpes, of the Ophthalmic Region, Ophth. Hosp. Rep. **6**:1-11, 1867.

3. Mules, P. H.: Paralysis of Third Nerve, with Unusual Complications, Tr. Ophth. Soc. U. Kingdom **21**:292-296, 1901.

4. Trousseau, A.: Clinique médicale de l'Hotel-Dieu de Paris, 2 ed., p. 287, Paris, J. B. Baillière et fils, 1862.

5. Rea, R. L.: Neuro-Ophthalmology, ed. 2, St. Louis, C. V. Mosby Company, 1941.

6. Edgerton, A. E.: Herpes Zoster Ophthalmicus: Report of Cases and Review of Literature, Arch. Ophth. **34**:40-62 (July); 114-153 (Aug.) 1945.

7. Head, H.: Herpes Zoster, in Allbutt, T. C., and Rolleston, H. D.: A System of Medicine, ed. 2, London, The Macmillan Company, 1910, vol. 7.

Burning, aching, pulling, drawing and boring are some of the terms used by patients to describe the pain, which is always present, but much worse at some times than at others. This discomfort appears spontaneously, but in some patients there is also a lancinating, ticlike pain which may be evoked by sensory stimulation of the usual trigger zones of true trigeminal neuralgia. Because of the persistence of this gnawing distress, many types of medical and surgical treatment have been tried.

Medical aids have included local use of oils and liniments and administration of opium tincture U. S. P., quinine (Hutchinson [8]), posterior pituitary U. S. P., acetylsalicylic acid, codeine, diacetylmorphine (Hamilton [9]), nicotinic acid and ferrous sulfate. Ultraviolet light, radiant heat and infra-red radiation have proved ineffective. Rea found thiosinamine (allyl thiourea) ethyl iodine of value when the postherpetic pain had not been of too long duration. Others (Walker and Walker [10]) have used diphtheria antitoxin, smallpox vaccine (Lillie [11]) and histamine (Horton [12]).

Bowman [2] cut the supraorbital nerve in one patient with persisting postherpetic pain and the supraorbital and infratrochlear nerves in another. The first had only temporary relief; the second appeared to obtain permanent benefit. Cushing [13] reported no relief from avulsion of the supraorbital nerve in two patients or from retrogasserian neurotomy in another. Harris [14] described success in three patients with postherpetic trigeminal neuralgia from injection of alcohol into the gasserian ganglion. Frazier and Russell [15] emphasized the importance of differentiation from typical tic douloureux, "for should a mistake be made not only will the patient not be relieved by the operation [retrogasserian neurotomy] but in all likelihood he will be worse." They noted the similarity in descriptive terms used by patients with postoperative paresthesias and the sensory phenomena of the atypical neuralgias, including postherpetic pain. Peet [16] obtained relief from lancinating postherpetic pain by retrogasserian neurotomy, but the dull aching pain persisted in both cases in which this was done. He did not advocate the operation for this condition.

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8. Hutchinson, J.: A Clinical Report on Herpes Zoster Frontils seu Ophthalmicus (Shingles Affecting the Forehead and Nose), Ophth. Hosp. Rep. **5**:191-195, 1866.

9. Hamilton, J. G. M.: Herpes Zoster, Practitioner **159**:122-127, 1947.

10. Walker, J. R., and Walker, B. F.: A Specific Treatment for Herpes Zoster, Arch. Ophth. **20**:304-306 (Aug.) 1938.

11. Lillie, W. I.: The Treatment of Herpes Zoster Ophthalmicus with Smallpox Vaccine, New York State J. Med. **43**:857-859, 1943.

12. Horton, B. T.: Symposium: Head and Face Pain: Medicine, Tr. Am. Acad. Ophth. **49**:23-33, 1944.

13. Cushing, H.: The Major Trigeminal Neuralgias and Their Surgical Treatment Based on Experiences with 332 Gasserian Operations: I. The Varieties of Facial Neuralgia, Am. J. M. Sc. **160**:157-184, 1920.

14. Harris, W.: Persistent Pain in Lesions of the Peripheral and Central Nervous System, Brit. M. J. **2**:896-900, 1921.

15. Frazier, C. H., and Russell, E. C.: Neuralgia of the Face: An Analysis of 754 Cases with Relation to Pain and Other Sensory Phenomena Before and After Operation, Arch. Neurol. & Psychiat. **11**:557-563 (May) 1924.

16. Peet, M. M.: Post-Herpetic Trigeminal Neuralgia: Persistence of Pain After Section of Sensory Root of Gasserian Ganglion, J. A. M. A. **92**:1503-05 (May) 1929.

Wood [17] used procaine for relief of pain which followed herpes zoster and, because of the beneficial results of the local injection, advocated avulsion of the peripheral nerve. Bailey [18] believed that the failure of trigeminal root section to give relief was analogous to the usual failure of dorsal root section to relieve postherpetic pain in the distribution of spinal nerves. He considered roentgen therapy to be the only effective treatment; he had obtained immediate and permanent relief from persistent postherpetic pain with roentgen irradiation. Reichert,[19] in 1936, described striking amelioration of the deep-seated burning, aching pain of postherpetic neuralgia by ablation of the sympathetic chain from the seventh cervical to the second thoracic ganglion, inclusive. When the age and physical status of the patient made this resection unfeasible, he used incision along the eyebrow, dividing all nerves and blood vessels, to interrupt the sympathetic fibers. Resection of the facial artery and vein and adjacent tissue was found to give marked relief of maxillary aching pain, and, to some extent, of the pain behind the eyeball. More recently [20] (1947) he has obtained relief of postherpetic supraorbital trigeminal neuralgia of the ophthalmic division in 10 patients by incising the shaved eyebrow down to the periosteum from the midline to the outer edge of the eyebrow.

Sjöqvist [21] also noted the failure of trigeminal root section to relieve the dull deep pain of postherpetic neuralgia. The third case in which he performed section of the trigeminal pathway in the medulla oblongata was for postherpetic pain in the eye and forehead. The operation did relieve the immediate severe pain, but there was persisting dull distress. He suggested that further attempts in similar cases might be directed toward the secondary trigeminal pathway. He linked herpetic neuralgia and the atypical pain following trigeminal root section for tic douloureux to involvement of the trigeminal nucleus. Olivecrona [22] further discussed the resemblance between the painful anesthesia following section of the fifth cranial nerve root and postherpetic neuralgia; he, too, pointed to the nucleus of the fifth cranial nerve as a possible site of the pathological process in both syndromes. He obtained no relief from complete root section, thoracocervical sympathectomy, stripping of the carotid artery or section of the spinal trigeminal tract. He considered division of the secondary trigeminal tract an attractive possibility but a formidable operation.

LeBeau, Daum and Forjaz [23] gave the histories of two patients with pain after ophthalmic zoster in whom Clovis Vincent, in 1940 and 1941, sectioned the quinto-

17. Wood, H.: Herpes Zoster Ophthalmicus Complicated by Persistent Neuritis, Am. J. Ophth. **12**:759-760, 1929.

18. Bailey, P.: Neuralgias of the Cranial Nerves, S. Clin. North America **11**:61-77, 1931.

19. Reichert, F. L.: Treatment of the Neuralgias of the Head and Face, Proceedings Second Congress Pan-Pacific Surgical Association, 1936, p. 183.

20. Riechert, F. L.: Personal communication to the authors, 1947.

21. Sjöqvist, O.: Studies on Pain Conduction in the Trigeminal Nerve: A Contribution to the Surgical Treatment of Facial Pain, Acta psychiat. et neurol., 1938, supp. 17.

22. Olivecrona, H.: The Syndrome of Painful Anesthesia Following Section of the Sensory Root of the Fifth Nerve in Tic Douloureux, Acta. chir. Scandinav. **82**:99-106, 1939.

23. LeBeau, J.; Daum, S., and Forjaz, S.: Les tractotomies trigeminales dans le traitement des nevralgies faciales, Brasil méd.-cir. **10**:331-344, 1948.

thalamic tract in the pons, after attack on the peripheral nerve had failed. The benefits were equivocal.

Glaser [24] included postherpetic trigeminal neuralgia in his discussion of atypical facial neuralgias. Of 245 patients with atypical neuralgia, there were four with postherpetic pain. All had pain in the ophthalmic division, and in each the scars of the vesicles were still present. He believed some measure of relief might be obtained from surgical proceedings on the sympathetic nervous system. Hyndman [25] also proposed this idea in 1942; he reported three cases of postherpetic pain of the face and neck eliminated by removal of the ipsilateral stellate and several upper thoracic ganglia. The irregular results of injection into the sphenopalatine or gasserian ganglion he ascribed to incomplete obliteration of varying numbers of afferent sympathetic fibers. Sympathectomy denervates the face, scalp and neck of these fibers. Since then (1947) he has done a cervicodorsal sympathectomy on eight patients with herpes zoster on or about the face, with 40 to 80 per cent benefit,

Results of Treatment of Postherpetic Trigeminal Neuralgia Reported by American Neurosurgeons in 1946

Therapeutic Technic	Surgeons Reporting Results: Little or No Relief	Much Relief But No Cure	Good Results or Cures	Totals
Retrogasserian neurotomy	29	2	2	33
Avulsion of supraorbital nerve	6	7	3	16
Alcohol injection into supraorbital nerve	6	3	0	9
Trigeminal tractotomy	4	3	0	7
Cervical sympathectomy	3	2	1	6
Stellate block	3	3	0	6
Roentgen irradiation to gasserian ganglion	1	0	1	2
Alcohol injection into gasserian ganglion	0	0	1	1
Totals	52	20	8	80

according to the patients' testimony, "but with never again what I considered a complete cure." [26]

Naffziger and Boldrey [27] and Peet and Echols [28] have decried the use of trigeminal rhizotomy for postherpetic pain. In general, this appears to be the opinion of most neurosurgeons. In 1946 one of us (P. C. B.) wrote to American neurosurgeons listed as certified by the American Board of Neurological Surgery, asking for résumés of their experiences with treatment of postherpetic trigeminal neuralgia. The table summarizes the data from those who replied.

24. Glaser, M. A.: Atypical Facial Neuralgia: Diagnosis, Cause and Treatment, Arch. Int. Med. **65**:340-367 (Feb.) 1940.

25. Hyndman, O. R.: Postherpetic Neuralgia in the Distribution of the Cranial Nerves: Evidence for Sympathetic Mediation and Surgical Cure, Arch. Neurol. & Psychiat. **42**:224-232 (Aug.) 1939.

26. Hyndman, O. R.: Personal communication to the authors, 1947.

27. Naffziger, H. C., and Boldrey, E. B.: Surgery of Spinal Cord, in Bancroft, F. W., and Pilcher, C.: Surgical Treatment of the Nervous System, Philadelphia, J. B. Lippincott Company, 1948.

28. Peet, M. M., and Echols, D. H.: Surgery of Disorders of Cranial Nerves, in Bancroft, F. W., and Pilcher, C.: Surgical Treatment of the Nervous System, Philadelphia, J. B. Lippincott Company, 1946.

In 1947, David and associates [29] sectioned the spinothalamic tract in the midbrain for intractable postherpetic pain in the distribution of the brachial plexus, with good results for the three days that their patient lived before dying of pneumonia. Guiot and Forjaz [30] used the subtemporal approach for mesencephalic tractotomy in a patient with ophthalmic herpes zoster; he died soon after the operation.

When one neurosurgeon reported on several procedures or varying results of one procedure, he has been counted in more than one column. Sixty-nine neurosurgeons reported that they either had had no experience with the treatment of postherpetic trigeminal neuralgia or knew of no good treatment.

Hamilton mentioned that occasionally injection of alcohol and trigeminal root section gave relief but that sometimes the pain recurred. In summarizing his 10 years' experience with trigeminal tractotomy, Sjöqvist [31] related the failure of the operation in two cases of postherpetic trigeminal neuralgia. He suggested prefrontal lobotomy as a possible solution for the painful paresthesias which follow trigeminal neuralgia. This had already been tried. LeBeau [32] recalled that he had seen a patient with continuous facial pain relieved by prefrontal lobotomy done by Jefferson at Manchester after the war. Falconer [33] reported amelioration of intractable postherpetic trigeminal neuralgia by bilateral prefrontal lobotomy. His patient, aged 70, had had procaine block of the gasserian ganglion, injection of alcohol at the foramen ovale, retrogasserian neurotomy, bulbar trigeminal tractotomy and procaine block of the upper thoracic portion of the sympathetic chain, as well as two treatments with electroconvulsive therapy. Watts and Freeman [34] did a lower frontal lobotomy for continuous facial neuralgia of an atypical variety in 1947. The woman, who had become addicted to narcotics, was relieved of her addiction and no longer mentioned the pain. Koskoff [35] has done lobotomies for relief of atypical constant facial neuralgias since as early as July 1946; in one patient unilateral lobotomy relieved the symptoms. Without doubt other surgeons have done similar operations which have not yet been reported. LeBeau, Bouvet and Rosier [36] ablated areas 9 and 10 of Brodmann in a patient with intractable postherpetic facial neuralgia, with therapeutic benefit for the five days that the woman lived.

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29. David, M.; Talairach, J., and Hecaen, H.: Étude critique des interventions neurochirurgicales actuellement pratiquées dans le traitement de la douleur, Semaine d. hôp. Paris **23**:1651-1665, 1947.

30. Guiot, G., and Forjaz, S.: La tractotomie mésencéphalique par voie soustemporale, Rev. neurol. **79**:733-740, 1947.

31. Sjöqvist, O.: Ten Years' Experience with Trigeminal Tractotomy, Brasil méd.-cir. **10**:259-274, 1948.

32. LeBeau, J.: La résection bilatérale de certaines aires corticales prefrontals (topectomie), Semaine d. hôp. Paris **24**:1937-1942, 1948.

33. Falconer, M. A.: Relief of Intractable Pain of Organic Origin by Frontal Lobotomy, A. Research Nerv. & Ment. Dis., Proc. (1947) **27**:706-714, 1948.

34. Watts, J. W., and Freeman, W.: Frontal Lobotomy in the Treatment of Unbearable Pain, A. Research Nerv. & Ment. Dis., Proc. (1947) **27**:715-722, 1948.

35. Koskoff, Y. D.; Dennis, W.; Lazovik, D., and Wheeler, E. T.: The Psychological Effects of Frontal Lobotomy Performed for the Alleviation of Pain, A. Research Nerv. & Ment. Dis., Proc. (1947) **27**:723-753, 1948.

36. LeBeau, J.; Bouvet, M., and Rosier, M.: Traitement des douleurs irreductibles par la topectomie, Semaine d. hôp. Paris **24**:1946-52, 1948.

Dr. Jefferson Browder and Dr. Everett G. Grantham have both had some success with relief of postherpetic pain by excision of the involved skin. Browder has obtained relief in some cases of ophthalmic herpes by making an incision down to the bone on all sides of the involved area except at the midline, and Dr. Robert Watson had excellent results in a similar case. He made an incision completely around the involved area except between the ear and the lateral margin of the orbit, reflected the scalp and removed all tissue between the galea and the periosteum, including the frontalis muscle, the supraorbital nerve and the temporal artery and its branches.

The case reported here demonstrates the variety of therapeutic endeavors used in attempting to relieve a man of postherpetic trigeminal neuralgia. It is the first reported instance of bilateral removal of portions of the postcentral cerebral cortex for relief of pain in the face.

REPORT OF A CASE

M. C., a white man aged 67, was admitted to the Illinois Neuropsychiatric Institute on March 11, 1946, because of intractable burning pain in the left eye and cheek and the left side of the nose, of nine months' duration. In July 1945 he had had a painful vesicular eruption of the skin involving the left cheek and the left side of the jaw. This was treated by local applications, without relief. The rash disappeared, but the pain persisted, being virtually constant, with burning and stinging, in the left eye, eyelids and upper part of the cheek and the left side of the nose, with episodes of lancinating pain in the upper part of the cheek and nasolabial fold on the same side.

In December 1945, injection of alcohol into the infraorbital nerve at the infraorbital foramen resulted in reduction of the number of attacks of lancinating pain. A course of roentgen irradiations of the gasserian ganglion was ineffective. In January 1946 partial division of the sensory root of the left trigeminal nerve was performed by the subtemporal approach. The ganglion was seen to be injected, granular and adherent to the neighboring dura mater. Alcohol was injected directly into the ganglion at that time. Postoperatively, there was subjective numbness of the entire left side of the face, but the stinging, burning pain persisted unabated. He was then transferred to the Institute for further observation and treatment.

Physical examination disclosed arterial hypertension (blood pressure, 188/120), peripheral and retinal arteriosclerosis and cardiac enlargement. There were analgesia in the domain of the third division of the left trigeminal nerve and weakness of the jaw muscles on this side. The tongue deviated somewhat to the right, with mild atrophy, and there was palatal weakness on the right. The left pupil appeared somewhat larger than the right. The results of all laboratory studies were within normal limits, as were the findings in the rest of the physical and neurological examinations.

Analgesics, such as codeine and inhalations of trichloroethylene, had little effect. On March 26 the gasserian ganglion was again exposed and again found to be granular. All root fibers were severed. For two days after this operation there was almost complete relief of pain, but the constant burning distress then appeared with all its former vigor, especially in the left nasolabial fold. Cocainization of the splenopalatine ganglion by an otorhinolaryngologist failed to relieve the pain, nor did procaine block of the stellate ganglion relieve the patient's complaints, although it did produce Horner's syndrome and a hot dry arm.

After presentation of the patient and his problem to the staff conference of attending neurologists and neurosurgeons, it was decided to undertake extirpation of the contralateral sensory cortex for the face (postcentral gyrus). There had been reported relief of the pain of a phantom limb from excision of the corresponding parietal somesthetic cortex (de Gutiérrez-Mahoney [37]), and it was thought proper to attempt relief of this burning deep constant pain by a similar technic. Accordingly, on April 18, with the patient under general anesthesia, a large osteoplastic craniotomy was performed in the right frontoparietal area. The procedure was sufficiently

37. de Gutiérrez-Mahoney, C. G.: The Treatment of Painful Phantom Limb by Removal of Post-Central Cortex, J. Neurosurg. **1**:156-162, 1944.

lengthy that it was thought best to delay the cortical extirpation. The bone flap was readily reelevated, with the use of local anesthesia, on May 3, and the surface of the brain was visualized.

The central fissure ran obliquely across the exposed field, approximately two fifths of the distance from the anterior to the posterior margins of the bony opening. Only the most posterior portion of the sylvian fissure was visible. The cerebral cortex and meninges were not grossly abnormal. Responses to electrical stimulation were obtained only from the precentral and postcentral gyri. The precentral cortex was stimulated first (bipolar electrodes; condenser discharges; current strength, 14 volts; falling phase of current, 1 sigma; frequency of stimulation, 2 to 5 per second). At a frequency of 5 stimuli a second, flexor movements of the left hand and fingers were obtained from the uppermost portion of the exposed gyrus. Movements of the tongue and jaw were driven at the frequency of (2) stimuli per second from the lower portion of the precentral gyrus. Stimulation of the postcentral gyrus with this frequency produced no motor or sensory manifestations. No sensory phenomena were induced from the precentral gyrus at any time. At a frequency of 60 stimuli a second and with a current strength

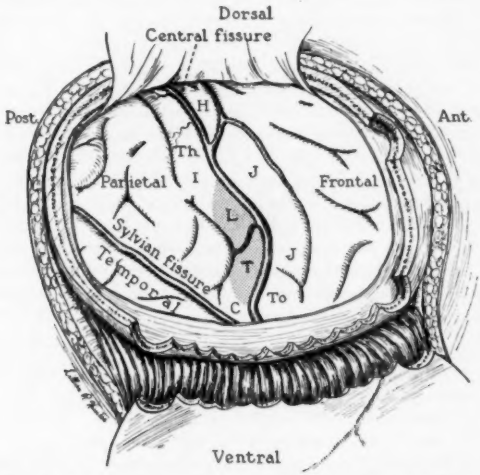

Fig. 1.—Diagram of right central region exposed at first operation (from drawing made at operation). Stimulation of precentral region with thyrotron stimulator, at 2 to 5 stimuli per second, 1 sigma falling phase, 14 to 20 volts; postcentral stimulation at 60 stimuli per second, 1 sigma falling phase, 8 to 12 volts. The dotted area corresponds to the extent of the cortical excision.

Stimulation at *C* produced irritation in throat and sensation of strangulation, causing "clearing" of throat; *H*, flexion of fingers of left hand; *I*, sensation in left index finger; *J*, opening and closing of jaws; *L*, sensation in left side of upper lip; *T*, sensation in left side of tongue and roof of mouth; *Th*, sensation in left thumb; *To*, movement of tongue.

of 8 volts, stimulation in the more superior portion of the exposed postcentral gyrus evoked sensation in the thumb and index finger of the left hand. Stimulation of the lower portions of the gyrus evoked sensations in the lips, the roof of the mouth and the left side of the tongue and jaw. From the most oral portion of the postcentral gyrus, just above the sylvian fissure and its vessels, there was evoked a sensation in the throat which caused the patient, apparently involuntarily, to clear his throat repeatedly. On one or two occasions, he said the sensation was one of strangulation. (These findings are summarized in figure 1.)

All of the postcentral gyrus between the representation of the thumb and index finger and that of the throat was then removed, the length of the area amounting to about 3 cm. (fig. 1). The extirpation was subpial and made in three portions, to avoid an artery which passed pos-

teriorly from the central fissure across the postcentral gyrus. After the extirpation was done, the cortex around the defect was again stimulated, with a current of 12 volts for the precentral and of 20 volts for the postcentral cortex. Sensations in the left thumb and index finger and the left side of the throat were again obtained. No sensations in the mouth or face were elicitable. The patient spontaneously offered the information that the persistent pain in the face had been completely relieved.

Immediately after operation it was noted that speech was thick, dysarthric and dyslalic. There was difficulty in swallowing, apparently due both to motor weakness and to sensory loss. There were slight weakness of the left arm and loss of pain perception in the thumb and index finger. Supranuclear facial paresis was conspicuous, but this, as well as the weakness of the arm, disappeared by the third postoperative day, and the dysarthria and difficulty in swallowing were much reduced.

On the fifth postoperative day neurologic examination revealed posterior and inferior extension of the superficial sensory loss present in the face since the retrogasserian neurotomy. Vibratory and deep pressure sensation were equally well perceived on the two sides of the face. The left side of the jaw was weaker than it had been before this operation. There was some hypesthesia in the left side of the oropharynx, as well as some perversion of taste on that side (food did not "taste right"). In tests, perception of taste was definitely diminished on the left half of the tongue; there was no disturbance of smell. The remainder of the examination gave results similar to those before the operation. On this day the patient declared that for the first time since the cortical operation there was slight stinging pain in the left ala nasi. By the twelfth day following operation the pain had spread to include all of its original locale, but was not as strong as it had been before the operation. The neurological status at this date was not much different from that which it had been a week before. The strength of the jaw muscles had returned to its former status; taste was still definitely, though slightly, reduced on the left, and there was slight reduction of sensation to touch in the posterior portion of the pharynx. The sensory loss over the face was intermediate between what it had been after the last neurotomy and what it was immediately after the cortical extirpation. An electroencephalogram showed no evidence of damage and was interpreted as being normal for the patient's age. He was discharged on the twelfth postoperative day.

Unfortunately, the pain persisted and increased, to attain at least its former intensity.

Because of the possibility of bilateral representation for facial sensation in man, as in animals,[38] it was considered proper to extirpate the ipsilateral sensory area as well. The patient was, therefore, readmitted to the hospital on Oct. 5, 1946. The pain of which he complained was extremely severe and constant in the nasolabial area, less severe under the eye and intermittent over the eye. The extent of his preoccupation with his distress is indicated by the document which he spontaneously prepared to illustrate his complaints, a portion of which is shown in figure 2. The left side of the throat felt "sore, as if nerves were bare." There was complete anesthesia over the entire trigeminal area with slightly variant margins for touch, temperature and thorn prick perception (fig. 3). Dilatation of the left pupil was still present. There were no signs of sensory loss below the face or other neurological findings of importance. On October 24, a large osteoplastic craniotomy was done in the left frontoparietal area, with the patient under thiopental and gas anesthesia, and on November 6 the flap was reelevated, with the use of local anesthesia.

Reflection of the dura mater revealed the sensorimotor cortex. The motor cortex anterior to the rolandic vein was readily identified by stimulation with bipolar condenser discharge. Movements were obtained from the tongue, neck, throat, lip and fingers (fig. 4). Large movements (turning of the head to the left and flexion of the elbow) were obtained from stimulation anterior to the motor cortex proper. Stimulation of the postcentral gyrus with strengths of up to 20 volts and with frequencies of 2 to 100 per second produced neither sensation nor movement. The portions of the gyrus lying behind the motor "face" area and part of the

38. Marshall, W. H.; Woolsey, C. N., and Bard, P.: Cortical Representation of Tactile Sensibility as Indicated by Cortical Potentials, Science **85**:388-390, 1937.

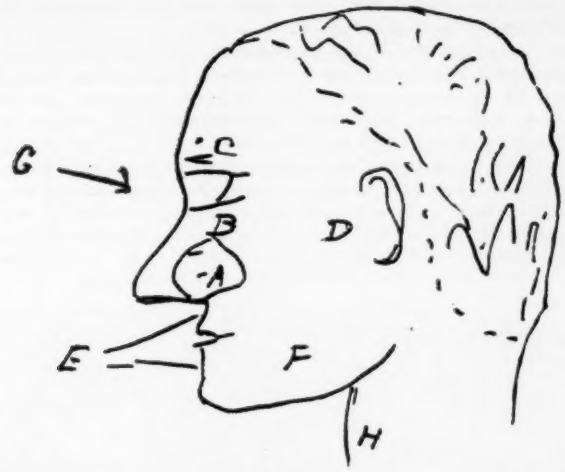

Fig. 2.—Photograph of drawing made by the patient, with notes describing his distress. *A* indicates "very severe pains all the time"; *B*, "very painful"; *C*, "very painful in spells"; *D*, "feeling like a pressure on ear drum"; *E*, "electric pains shooting through chin and lips"; *F*, "jaws very sore and painful"; *G*, "shooting pains through left eye"; *H*, "left side of throat sore as if nerves were bare. Cold drink, when it touches throat, seems to go up and around side of nose and cheek."

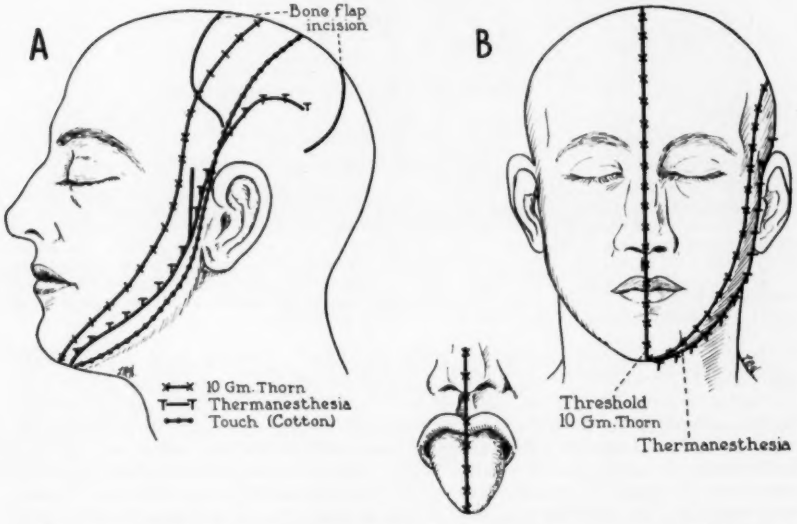

Fig. 3.—*A*, side view; *B*, front view. Diagrams of extent of sensory loss following trigeminal neurotomy and contralateral extirpation of sensory cortex. The straight vertical line in front of the ear delimits the incision for retrogasserian neurotomy. The bone flap incision is that for the second cortical extirpation.

"finger" area were then removed (fig. 4) by subpial resection. The patient was then given thiopental anesthesia for closure of the wound.

Microscopic examination of the tissue removed at the first operation revealed the structure of the postcentral gyrus, with granular cortex (PB of von Economo) on one face of the excised portion, shading into postcentral cortex (PC). The tissue removed at the second operation proved to have no koniocortex but contained granular cortex with narrow bands of small pyramidal cells, similar to area PF of von Economo.

The patient readily recovered from the surgical procedure, but the pain in the face was still present on awakening. There were no signs of motor involvement and no stereognostic loss in the right side of the face. Deep pressure and vibratory perception was intact bilaterally. Perception of figure writing was intact, and no sequelae of the operation could be noted in the neurological examination. An electroencephalogram recorded on November 19 was reported to be normal in frequency with minimal slowing in the right parietal area.

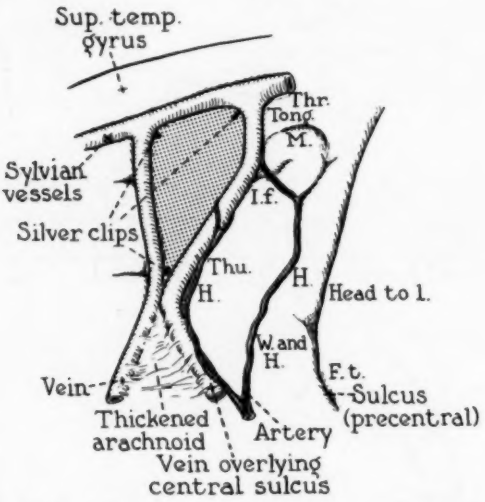

Fig. 4.—Diagram of left central region, from drawing made at operation. Motor cortex was stimulated with bipolar electrodes, thyrotron stimulator, at 2 stimuli per second, 0.2 sigma falling phase and 14 volts, and at 60 impulses per second with 4 volts. Stimulation of the postcentral cortex, at 2, 60 and 100 stimuli per second, 4 to 20 volts and 0.1 to 0.5 sigma falling phase, was without effect. The dotted area corresponds to the extent of the cortical excision. Stimulation of *F. t.* produced tremor of the forearm; *H.*, movements of hand; *Head to l.*, turning of head to left. *I. F.* shows area for index finger; *M.*, mouth; *Thr.*, throat (swallowing); *Thu.*, thumb; *Tong.*, tongue, and *W. and H.*, wrist and hand.

Because of the patient's continuing pain and agitation, suicidal thoughts and ruminative and depressive tendencies, it was decided to give electric shock therapy. A total of 10 grand mal and six abortive seizures were produced from Nov. 29 to Dec. 23, 1946. The patient developed an attitude of indifference toward the pain, which, however, was said to be still present when he was asked directly. He required no analgesics for over two weeks. On discharge, on December 23, he was free of pain for the first time in over a year. However, a few days after discharge he had recurrence of aching pain in the left side of the face, with sharp burning sensations in the left nasolabial area and left alveolar area. This grew to proportions sufficient to induce him to return to the hospital on March 14, 1947. There were still an enlarged left pupil and good anesthesia in the distribution of the left trigeminal nerve. The movements of the tongue were normal, but taste was still impaired on the left. He complained most when asked about his pain and required no analgesics. He did not appear as depressed as when he

was last hospitalized and said that his memory was better than it had been for a few years. He refused further operative treatment (prefrontal lobotomy was suggested) and was discharged on March 24, 1947, to be followed by Dr. K. G. McKenzie of Toronto, Canada. By the courtesy of Dr. McKenzie we give the following account of the further events in this case.

On May 28, 1947, bilateral prefrontal lobotomy was performed at the level of the posterior margins of the orbital plates. There was complete anesthesia over the three divisions of the left side of the face. No interference with perception of cold, pinprick or light touch could be made out over the right side of the face. The patient still complained of his steady burning pain, but only when asked directly; he did not introduce the subject spontaneously, and even when discussing it he looked cheerful and unconcerned. His memory remained good. He was well dressed and tidy, moved about public transportation by himself, read the papers and otherwise seemed quiet. When his wife was last interviewed (on Oct. 26, 1948), she stated that,

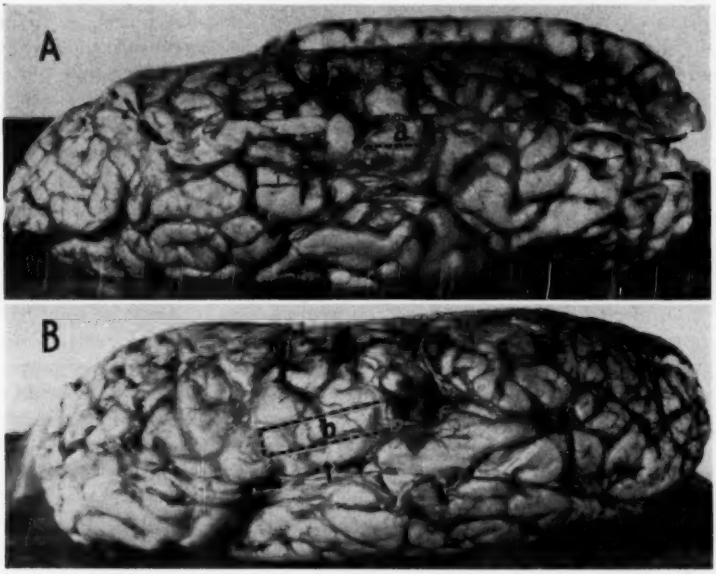

Fig. 5.—Photographs of lateral aspect of (*A*) the right and (*B*) the left cerebal hemisphere. The dotted area *a*, just anterior to the zone of cortical excision, proved to be precentral cortex. The dotted area *b*, anterior to the zone of cortical incision, proved to contain gyri in front of and behind the central sulcus, which is indicated by the arrow.

although her husband still had pain, he was much more cheerful about it, in contrast to his melancholy and threats of suicide which preceded the prefrontal lobotomy. "The pain does not seem to bother him the way it used to." She stated that he was much easier to live with, but had lost his initiative and was content to allow her to make the decisions and run the establishment, as he had not been before the difficulty started.

On Jan. 4, 1949, the patient fell against a door at his home; he died an hour later. His relatives reported that at that time he was still suffering from pain, although it was not as troublesome as it had been. Postmortem examination was made. Dr. Eric A. Linell, of the University of Toronto, supplied the following information. Figure 5 shows photographs of the lateral aspect of the brain. A block of tissue taken from the area immediately anterior to the zone of cortical excision on the right side was sectioned and found to have the structure of the precentral gyrus. The excision in the left cerebral hemisphere appears to have been in the gyrus

behind the lower end of the postcentral gyrus. A block of tissue taken anterior to this excision area crossed the central sulcus, as shown by the histological differences between the zone in front of and that behind the sulcus.

COMMENT

Precedent for the removal of the cortical area corresponding to the somatic area in which pain was felt came from the pioneer work of de Gutiérrez-Mahoney [37] (1944). By 1948 he had described [39] four cases with removal of the postcentral cortex for painful phantom limb and concluded that the operation was only partially effective in controlling the discomfort. Horrax [40] reported four cases of cortical excision for intractable pain, with varying results. He agreed with Walker [41] that cortical lesions may produce varying degrees of hypalgesia, from practically no impairment to severe loss of appreciation of pain. Echols and Colclough [42] relieved a painful phantom limb by cortical resection. On the other hand, Lhermitte and Puech [43] produced only temporary disappearance of a phantom limb by resection of the parietal lobe. David and associates [29] resected the parietal sensory cortex for phantom limb and clonic movements of the stump; unfortunately, their patient died four days after the operation in status epilepticus.

Odom and Lyman [44] removed the right postcentral (sensory) area for face and arm for relief of burning pain in the left side of the face in a left-handed woman of 68. The pain did disappear, except for pain in the left orbit, and there was loss of sensation in the face and arm. There was also a speech disorder, termed cortical ataxic dysarthria, paralleling the ataxia which occurred in the arm. In our case, after removal of the right postcentral face region in a right-handed man, there were thick, dysarthric and dyslalic speech and slight weakness of the left arm, as well as supranuclear facial paresis. All these phenomena disappeared save some weakness of the left side of the jaw, within five days. This would tend to support the suggestion that the speech disorder in Odom and Lyman's patient was due to circulatory disturbance in nearby regions rather than to removal of postcentral influence of pyramidal control of the speech organs.

Exactly what disturbance is responsible for the pain which follows herpetic infections is unknown. For a long time it was believed that the only lesion was that found in the posterior root ganglion (or in the gasserian ganglion in the case of postherpetic trigeminal neuralgia). This seems not to be true in at least some cases. The posterior gray columns may be affected, with hyperemia, hemorrhages and cellular infiltration, and in some cases inflammation can be found in the

39. Gutiérrez-Mahoney, C. G.: The Treatment of Painful Phantom Limb, S. Clin. North America 481-483, 1948.

40. Horrax, G.: Experiences with Cortical Excisions for the Relief of Intractable Pain in the Extremities, Surgery **20**:593-602, 1946.

41. Walker, A. E.: Central Representation of Pain, A. Research Nerv. & Ment. Dis., Proc. (1942) **23**:63-85, 1943.

42. Echols, D. H., and Colclough, J. A.: Abolition of Painful Phantom Foot by Resection of the Sensory Cortex, J. A. M. A. **134**:1476-1477 (Aug. 23) 1947.

43. Lhermitte, J., and Puech, P.: L'algo-hallucinose des amputés: Traitement par la résection du névrome, l'infiltration de la chaine sympathique, une double myélotomie postérieure, la résection du lobule parietal superieur, Rev. neurol. **78**:33-35, 1946.

44. Odom, G. L., and Lyman, R. S.: Speech Disorder Following Excision of Post-Central Gyrus, Tr. Am. Neurol. A. **71**:67-70, 1946.

anterior horns of the spinal cord (O'Donnell [45] and Denny-Brown and others [46]). Guillaume [47] attributed the effectiveness of posterior myelotomy (after posterior rhizotomy had failed to relieve postherpetic neuralgia) to the severance of pathways leading from the posterior horn cells. These cells he believed also to have been infected by the virus. Thalheimer [48] reported encephalitis from herpes zoster in a woman aged 72 who had had very severe pain following herpes zoster over the cervical region. Perivascular infiltrations were noted in the cervical portion of the cord, the medulla oblongata, the pons and as far as the internal capsule, but not in the substantia nigra. In the cervical portion of the cord the lesions were widespread. Wohlwill [49] and Denny-Brown and associates [46] also showed the extensiveness of lesions in the central nervous system in herpes zoster. Glaser [24] suggested that the persisting pain might be due to extension of the infection from the gasserian ganglion into the thalamus. Others (Bailey,[18] Craig,[50] Frazier and Russell,[15] Peet and Echols [28]) have long held that there was a central origin for the persisting postherpetic pain. Hyndman [25] believed it possible that the pain was due to sympathetic involvement, perhaps in the same way that causalgic pain appears to involve the sympathetic nervous system.

The striking thing about postherpetic pain appears to us to be its occurrence in elderly persons, and almost exclusively in those with signs of arteriosclerosis. Lewy and Grant [51] pointed out the separation of the facial and bodily representations in the thalamic syndrome and indicated the possibility that trigeminal neuralgia may be a form of thalamic syndrome restricted to the face. It seems possible that there is some perpetuation of pain in self-contained circuits in the thalamus. Ordinarily, painful stimuli arrive in the thalamus and are dispersed therefrom (to the various cortical areas); reentering corticothalamic circuits are of insufficient intensity to reactivate the thalamic nuclei. In the presence of arteriosclerosis with attendant mild hypoxia, it would be possible to have sufficiently lowered threshold that the reentering circuits could again activate the thalamic cells, to reinstitute pain. According to such a hypothesis, resection of the postcentral (sensory) cortex would remove but a small portion of the projection area which is involved in the thalamocorticothalamic circuit and might well be insufficient. Surgical therapy might then be a quantitative affair—if sufficient thalamic projection areas were removed, the patient might find relief. This might be the reason behind the effectiveness of topectomy and prefrontal lobotomy in cases of intractable facial

45. O'Donnell, J.: Posterior Ganglionitis with Anterior Poliomyelitis, Irish. J. M. Sc. (5th ser.) 122-124, 1923.

46. Denny-Brown, D.; Adams, R. D., and Fitzgerald, P. J.: Pathologic Features of Herpes Zoster: A Note on "Geniculate Herpes," Arch Neurol. & Psychiat. **51**:216-231 (March) 1944.

47. Guillaume, J.: Myélotomie postérieure pour algies postzostériennes et moignons douloureux avec membres fantômes: Remarques physio-pathalogiques, Rev. neurol. **74**:317-319, 1942.

48. Thalheimer, W.: Herpes Zoster: Central Nervous System Lesions Similar to Those of Epidemic (Lethargic) Encephalitis, Arch. Neurol. & Psychiat. **12**:73-79 (July) 1924.

49. Wohlwill, F.: Zur pathologischen Anatomie des Nervensystems beim Herpes zoster (auf Grund von zehn Sektionsfällen), Ztschr. f. d. ges. Neurol. u. Psychiat. **89**:171-212, 1924.

50. Craig, W. M.: Typical and Atypical Neuralgia of the Face and Neck, Proc. Staff Meet., Mayo Clin. **11**:677-681, 1936.

51. Lewy, F. H., and Grant, F. C.: Physiopathologic and Pathoanatomic Aspects of Major Trigeminal Neuralgia, Arch. Neurol. & Psychiat. **40**:1126-1134 (Dec.) 1938.

pain. Such a hypothesis might account, also, for the persisting pain following rhizotomy for trigeminal neuralgia. It is of interest in this connection that Furtado and Carvalho [52] reported beneficial effects from injections of nicotinic acid in patients with trigeminal neuralgia, although in our experience the benefit has been temporary and restricted to the flushing period and the time immediately thereafter. If the effectiveness of the substance does depend on its ability to dilate cerebral vessels, it is clear that in the presence of sufficient arteriosclerosis no vasodilatation could occur and hence the drug could not be uniformly effective.

The degree of sensory loss following ablation of the postcentral cortex is apparently variable. We could not test the left side adequately in our patient, owing to his preliminary peripheral operations. It is of interest, however, that at the time of stimulation sensations (vaguely described, to be sure) were evoked in areas which were completely anesthetic to pinprick, touch and temperature. Although the comparable area was exposed on the opposite (left) side at the second operation, stimulation would not give similar sensory phenomena. We are at a loss to explain this; electrical stimulation experiments apparently indicated the motor cortex, and the area removed was believed to be the region immediately posterior to the motor cortex. Histological analysis of the material removed at operation indicates, and the postmortem findings confirm the assumption, that it was not the postcentral gyrus which was removed.

The retention of perception of deep pressure and vibration even after peripheral denervation is not well understood. However, by their nature, the related stimuli for these sensations cannot be well localized; the vibration of a tuning fork is transmitted to various parts of the skull beyond the domain of the trigeminal nerve, while firm pressure on the bones of the skull is associated with strains on bones, ligaments and muscles of the neck that might readily produce some sensation. Certainly, one must postulate pathways other than through the trigeminal nerve. A complicating factor in the explanation of sensory perception after resection of the postcentral cortex is the existence of a second somatic sensory area (at least in monkeys and in lower animals), as described by Woolsey and associates,[53] lying in the parietal operculum. Near here, too, is apparently the cortical representation of taste. Börnstein [54] has located this area in Brodman's area 43 (i. e., the base of the postcentral gyrus). Shenkin and Lewey [55] contributed further suggestive evidence of such a localization in their case of angiomatous malformation in the sylvian fissure. After the first operation in our patient, there was subjective perversion of taste perception in the left side of the tongue, and objectively the patient had a definite diminution in perception of sweet and salt. On the other hand, no such loss of taste was noted after the second operation; this was apparently due to the removal of cortex posterior to the supposed taste center. It is of interest that the

52. Furtado, D., and Carvalho, O.: L'acide nicotinique dans la thérapeutique neurologique, Arch. suisses neurol. et psychiat. **57**:290, 1946.

53. Woolsey, C. N., and Fairman, D.: Contralateral, Ipsilateral, and Bilateral Representation of Cutaneous Receptors in Somatic Areas I and II of the Cerebral Cortex of Pig, Sheep, and Other Mammals, Surgery **19**:684-702, 1946.

54. Börnstein, W. S.: Cortical Representation of Taste in Man and Monkey: II. The Localization of the Cortical Taste Area in Man and a Method of Measuring Impairment of Taste in Man, Yale J. Biol. & Med. **13**:133-156, 1940.

55. Shenkin, H. A., and Lewey, F. H.: Taste Aura Preceding Convulsions in a Lesion of the Parietal Operculum (Case Report), J. Nerv. & Ment. Dis. **100**:352-354, 1944.

removal of the cortex just posterior to the first sensory cortex had no evident results, either in regard to aphasia or in regard to the integration of sensory impulses from the right side of the face. The excision was too superficial to have damaged the deeper subcortical pathways which are important in language function.

Our experience emphasizes again the difficulties in accurate localization of portions of the cerebral cortex exposed at the time of operation and the necessity for adequate histological control of procedures involving the cerebral cortex.

It is obvious from this study of the literature, our case and the responses to the questionnaire, that there is as yet no satisfactory solution to the problem of postherpetic pain, although the peripheral operations of Browder and Watson give promise in suitable cases. It is quite generally agreed that attacks on the peripheral innervation of the face can at best relieve only the paroxysmal sharp pains which may be precipitated by stimulation of the face. The very annoying, persistent, spontaneous aching, burning pain is not benefited by any attack on the trigeminal nerve or its spinal root in the medulla oblongata. Destruction of the sympathetic innervation is likewise ineffective. Bilateral frontal lobotomy has most frequently brought relief. The undesirable loss in personality and behavior attendant on frontal lobotomy makes that procedure one of desperation only. The loss of one's initiative, spontaneity and ambitions is a high price to pay for relief from pain. A vegetative existence is never desirable and is acceptable only as a last resort in the search for relief from pain which is worse than death.

SUMMARY

Postherpetic trigeminal neuralgia is a distressing condition which has been resistant to all forms of medical and surgical therapy until the recent advent of frontal lobotomy and related operations.

A case is reported in which various procedures were used in an attempt to relieve pain. Bilateral extirpation of cerebral cortex behind the central sulcus failed to give relief. After the failure of electric shock to give permanent freedom from pain, bilateral frontal lobotomy gave some surcease.

Evidence is adduced from the findings in this case in favor of a localization of the projection area for taste at the foot of the postcentral gyrus.

A hypothesis is offered to explain the persistence of pain after section of the afferent pathways to the thalamus, depending on lowered threshold at synapses due to hypoxia attendant on cerebral arteriosclerosis.

TUBERCULOMAS OF THE BRAIN

Report of One Hundred and Fifty-Nine Cases

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H. VALLADARES, M.D.
AND
J. FIERRO, M.D.
SANTIAGO, CHILE

MORE than three years ago one of us (A. A.) and associates [1] published a report of 100 patients with tuberculoma of the central nervous system who has been treated in the Instituto Central de Neurocirurgia and Neuropatologia, up to July 1945 and we stated at that time that "with the progress of the methods of diagnosis and of neurosurgery and with the benefit of the medical treatment of tuberculosis, we are able to look ahead with more encouragement; the outlook stimulates our perseverance and challenges us to attempt more daring surgery." Little time has passed since the introduction of streptomycin, paraaminosalicylic acid and the sulfonamide drugs has obliged us to change our clinical and therapeutic procedure in the attack on this problem.

According to Davis [2] and Bailey,[3] tuberculomas constituted 50 per cent of the new growths of the central nervous system at the close of the last century. Starr [4] (1889) saw 41 tuberculomas in 300 cases of tumors of the brain in adults and stated that this proportion increased in childhood and youth to 152 tuberculomas in 300 cases. Tooth's [5] statistical data, covering a period from 1902 to 1912, showed five tuberculomas in 187 brain tumors. Bruns [6] (1908) observed 10 tuberculomas in 63 autopsies, nine of which occurred in children. Elsberg [7] (1931), among 767 cases of tumor, found nine granulomas, and Cushing's [8] famous statistics revealed 33 tuber-

From Instituto Central de Neurocirurgia y Neuropatologia; Director, Prof. Dr. A. Asenjo.

1. Asenjo, A.; Perino, F. R.; Garcia, E., and Gallo, A.: Cien casos de tuberculomas del sistema nervioso central, Rev. méd. de Chile **75**:1-16, 1947.

2. Davis, L.: The Principles of Neurological Surgery, ed. 2, Philadelphia, Lea & Febiger, 1942.

3. Bailey, P.: Intracranial Tumors, ed. 2, Charles C Thomas, Publisher, Springfield, Ill., 1948.

4. Starr, A.: Tumours of the Brain in the Children: Their Variety and Situation, with Special Reference to Their Treatment by Surgical Interference, M. News, Philadelphia, **54**:29-37, 1889.

5. Tooth, H. H.: Some Observations on the Growth and Survival-Period of Intracranial Tumours, Brain **35**:61-108, 1912-1913.

6. Bruns: Die Geschwülste des Nervensystem: Hirngeschwülste; Rückenmarks-und Wirbelgeschwülste; Geschwulste der peripheren Nerven, Berlin, S. Karger, 1908.

7. Elsberg, C. A.: The Meningeal Fibroblastomas, Bull. Neurol. Inst. New York **1**:3-27 and 579-592, 1931.

8. Cushing, H.: Intracranial Tumours: Notes upon a Series of Two Thousand Verified Cases with Surgical-Mortality Percentages Pertaining Thereto, Springfield, Ill., Charles C Thomas, Publisher, 1932.

culomas in 2,023 cases of intracranial tumors. Of the last 412 tumors, which were operated on between 1928 and 1931, four were granulomas. Tönnis [9] (1938) diagnosed seven tuberculomas in 638 verified tumors of the brain, and one year later, at the meeting of the British Society of Neurosurgeons, a report was made on 94

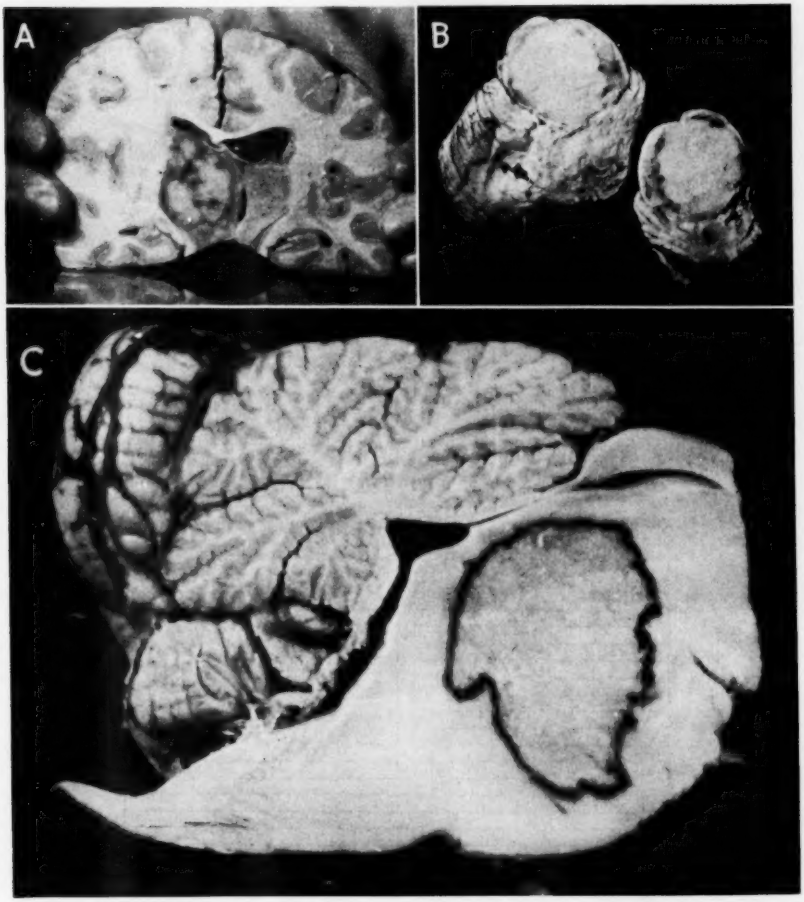

Fig. 1.—*A* (case 690; a student aged 23), nodular tuberculoma occupying the entire right side of the thalamus and growing in serpiginous form. The corresponding cerebral hemisphere was enlarged because of edema.

B (case 2523), tubercle 3 cm. in diameter, occupying the whole pons and transforming the brain stem into a thin capsule, with cerebral edema and herniation of the cerebellar tonsils. In spite of the site and the size of the lesion, the patient did not present papilledema.

C (case 2805), tuberculoma of the region of the pons.

9. Tönnis, W.: Über Hirngeschwülste, Ztschr. f. d. ges. Neurol. u. Psychiat. **161**:114-148, 1938.

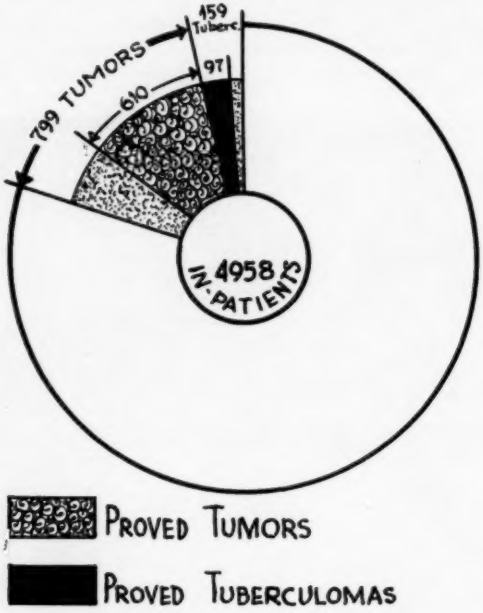

Fig. 2.—Graph showing comparative frequencies of tumors and tuberculomas, both verified and unverified, in 4,958 hospitalizations (up to Dec. 31, 1949).

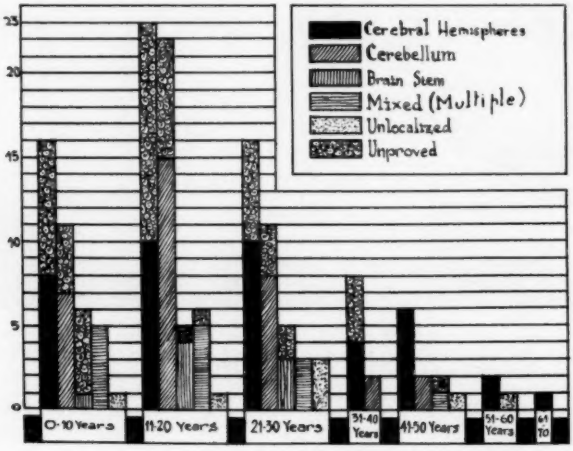

Fig. 3.—Distribution according to age and localization.

tuberculomas from the neurosurgical clinics in England, as cited by Imaginario. Wilson [10] (1940), in a series of 2,190 tumors gathered from the literature of that time, found that 3.6 per cent were tuberculomas. We may state, then, that the percentage of tuberculomas in relation to cerebral malformations in Anglo-Saxon countries varies at present from 1.5 to 3.6 per cent.

In France, Thiebaut [11] (1939) stated that tuberculomas represent one seventh of the cerebellar and one tenth of the cerebral tumors, with a total of 12 per cent. Obrador [12] (1948), collecting data on incidence from various Spanish neurosurgeons, cited a frequency of 7 per cent and Imaginario,[13] of Portugal, found at the same time that tuberculomas comprised 6 per cent of 500 cerebral malformations.

In order better to appreciate the material to be presented, as well as the foregoing statistics, it must be noted that autopsy is not compulsory in the services in most of the aforementioned countries. There are no social security laws or worker's insurance which cover a large part of the population, as in Chile, nor is there centralization of neurological patients, so that cases of this lesion are disclosed, especially those in which increased intracranial pressure is suspected. Furthermore, with regard to tuberculosis, Chile is passing through an epidemiological phase, similar to that which was experienced in the Anglo-Saxon countries during the middle and the end of the last century.

The present paper covers the study of 4,958 patients admitted to the Institute from Feb. 26, 1940 to Dec. 31, 1949 (fig. 1). In this series we found 159 cases of tuberculoma, an incidence of 3.20 per cent, 97 of which were verified. Tuberculoma was found in 15.90 per cent of the 610 cases of verified tumors. Among the 799 cases of verified and nonverified tumors, there were 159 cases of tuberculoma, or 19.89 per cent.

Anatomic distribution according to age is shown in figures 2 and 3.

We shall review the cases in accordance with the following heads: (1) general pathogenetic factors; (2) relation to pulmonary lesions; (3) pathological features; (4) symptoms; (5) diagnosis; (6) treatment; (7) prognosis.

GENERAL PATHOGENETIC FACTORS

The age distribution (figs. 1, 2 and 3) varied from 19 months to 70 years. We repeat that Chile is in a stage of tuberculization in which the biologic, or natural, defense is not yet available. This fact is still more apparent among the small group of aborigines and mestizos, representing 8 per cent of the population. It is the people from the country, with no previous contact with factories and cities, who are easily tuberculized when, owing to the present stage of industrialization of the country, they move into the cities. During the last 10 years, however, there has been great improvement in their condition. It must be noted that the living conditions of the working class with regard to such factors as food, housing and alcoholism lessen the possibility of acquired defenses.

10. Wilson, K.: Neurology, Baltimore, William Wood & Company, 1940.

11. Thiebaut, F.: Tuberculose cérébrale: les tubercules cérébraux, Encyclopédie médico-chirurgicale **17054**:1-7, 1939.

12. Obrador, S.; Urquiza, P., and Albert, P.: Algunos aspectos neuroquirúrgicos de la tuberculosis encefálica, Rev. españ. oto-neuro-oftal. y neurocir. **8**:105-130, 1949.

13. Imaginario, J.: Tuberculos intracraneanos, Rev. españ. oto-neuro-oftal. y neurocir. **8**:88-92, 1949.

A history of contact with tuberculous persons in the family is important. In 44 cases there was definite proof of family contact, and in 11 others it was strongly suspected.

A survey of the extraneural occurrence showed a definite tuberculous lesion in 86 cases, with the following distribution: pulmonary or pleural, 62 cases; extrapulmonary and nonencephalic, 9 cases; osteoarticular, 4 cases; orchiepididymitis, 2 cases; peritoneal, 1 case; ganglionic, 2 cases; mixed extrapulmonary and intrapulmonary, 15 cases.

TABLE 1.—*Tuberculous Pulmonary Lesions in Cases of Tuberculomas of the Brain Verified at Autopsy*

			Localization of the Tuberculomas *			
			Cerebellum	Hemisphere	Stem	Mixed
Total no. of autopsies reviewed 49 (presence of tuberculoma proved in all cases)	Normal lungs	7	846	51; 4667	2567	584; 73; 741
	Pulmonary tuberculosis	42	507; 639; 2111; 257; 555; 1587; 664; 704; 2665; 973; 474; 4314; 1039; 1211; 1319	349; 642; 1284; 183; 201; 2663; 339; 1667; 2805; 3144; 3416; 3830; 4926	1181; 2523; 2688	883; 1529; 1935; 1366; 2159; 2530; 1132; 2520; 4132; 4230; 4906
Roentgenographic (3) and roentgenoscopic (3) examinations in addition to autopsies without pulmonary tuberculosis	Normal lungs with normal roentgenogram	3	.....	.....	2567	584; 73
	Normal lungs with normal roentgenoscopic findings	3	846	4667	....	741
Roentgenographic (24) and roentgenoscopic (14) studies in addition to autopsy with pulmonary tuberculosis	Pulmonary tuberculosis with normal roentgenogram	3	704	3830	....	2159
	Pulmonary tuberculosis with positive evidence in roentgenogram	21	257; 555; 597; 664; 973; 474; 1211; 1587; 1039	183; 339; 349; 642; 2805; 3144	2523; 2688	1366; 1935; 2159; 1132
	Pulmonary tuberculosis with normal roentgenoscopic findings	4	704; 211	.....	1181; 2523	.....
	Pulmonary tuberculosis with positive roentgenoscopic findings	10	973; 1211; 1319; 1587	183; 2663	....	2530; 1132; 4132; 4230

* Numerals correspond to case numbers.

RELATION TO PULMONARY TUBERCULOSIS OF TUBERCULOMAS OF THE BRAIN

The respiratory tract is the portal of entrance of infection in most cases, and since the disease most commonly affects the thoracic cavity, we have made studies of the incidence of pulmonary infection in our cases.

Of 49 cases in which autopsy confirmed the presence of cerebral tuberculomas, roentgenographic examination, which was made in all, showed no lesions in the lungs in seven. Of the 42 cases with pulmonary signs, roentgenologic study (24 cases) did not reveal lesions in the lungs in three, and roentgenoscopic studies (14 cases) failed to show pulmonary involvement in four and revealed lesions in the lungs in 10. In connection with this statement, we must point out that the autopsies of the affected lungs were made at the Instituto de Anatomopatologia del Hospital del Salvador, and the brain sections were made at the Instituto de Neurocirurgia by the neuropathologist, together with the neurosurgeon, with suitable technic.

The comparative results of roentgenographic and roentgenoscopic studies in 47 cases of tuberculoma may be seen in table 2.

The relation of the type of pulmonary lesions diagnosed roentgenologically in the cases of cerebral tuberculoma is shown in table 3, the classification having been made with the assistance of the tuberculosis service (Prof. H. Orrego). Attention is called to the high proportion of hematogenous reinfection and to the roentgenographic evidence of pulmonary tuberculosis in 12 of 70 cases of cerebral tuberculoma. It is important to emphasize that in 12 cases the symptoms of increased intracranial

TABLE 2.—*Comparative Results of Roentgenoscopic and Roentgenographic Studies in Forty-Seven Cases of Tuberculoma*

	Proved by Autopsy or Surgery		Clinical Diagnosis Only	
	Total	Case No.*	Total	Case No.*
Normal roentgenoscopic and positive roentgenographic findings	5	753; 690; 1395; 1765; 2523	3	626; 2005; 2470
Positive roentgenoscopic and positive roentgenographic evidence	24	530; 973; 1637; 1211; 1587; 2030; 3072; 3377; 3914; 2311; 183; 2470; 2805; 3144; 3820; 343; 3864; 4138; 2646; 2688; 307; 1132; 3920; 4132	7	208; 1060; 1754; 881; 1966; 2266; 2202
Normal roentgenoscopic and normal roentgenographic findings	7	2839; 2888; 4314; 2102; 2392; 2567; 584	1	1297
Total.....	36		11	

* Numerals correspond to case numbers.

TABLE 3.—*Types of Pulmonary Lesions in Cases of Cerebral Tuberculomas* *

		Total	Cerebellum	Hemisphere	Brain Stem	Mixed	Unlocalized
Normal roentgenograms.....		12	704; 2888; 4314	217; 321; 467; 2839	2567	73; 1297; 2150; 584	.....
Inactive lesions.....		8	479; 3130	339; 1395; 1765; 1966	119; 640	.....	.....
Pleurisy only.....		4	2030	626; 1766; 2266	...	.....	.....
Primary and postprimary lesions.....		11	753; 973; 1150	642; 2005; 4230	307	1366; 4906	1548; 4669
Hematogenic form of reinfection, 20	Minimal.....	3	597	2470	...	2346	.....
	Moderate....	6	851	2311; 2668	2523	2202	804
	Advanced....	11	555; 771; 1039; 1211	623; 3144; 4926	...	1132	1076; 1392
Nonhematogenic form of reinfection, 15	Minimal.....	6	208; 1561	343; 1754; 3416	...	.....	1480
	Moderate....	7	257; 1587; 691; 1637; 2730	3373	2688	.....	.....
	Advanced....	2	1090	349	...	.....	.....

* Numerals in columns 3 to 7 correspond to case numbers.

hypertension appeared after tuberculous pleurisy, the time of onset varying from three months to three years.

Confronting this problem, we reaffirm our previous statements [1]: 1. The finding of undamaged lung on roentgenologic examination does not rule out conclusively the clinical or surgical diagnosis of tuberculoma of the nervous system.

2. From a pathogenetic point of view, we can assume the possibility, even though remote, of a nonpulmonary primary tuberculous lesion.

3. With regard to the prognosis, it is especially interesting to know the features, degree and extent of the extraneural tuberculous disease.

PATHOLOGICAL FEATURES

Figure 4 shows that there were 64 cases of single tuberculoma and 33 cases of multiple tuberculoma or tuberculoma of mixed localization. This incidence shows the possibilities of surgical treatment of the condition.

We have observed that the course of the growths attached to the meninges is more benign than that of tuberculomas located in the encephalon and that in Chile calcified tuberculomas are rare. In some cases we have seen granular ependymitis,

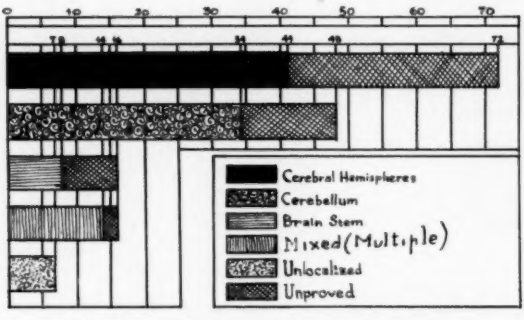

Fig. 4.—Distribution according to localization.

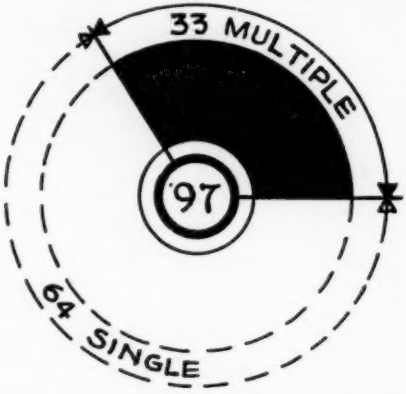

Fig. 5.—Distribution of multiple and single cerebral tuberculomas.

as well as granular choroiditis, with no specific tuberculous lesions; but in others we have observed microscopic tuberculomas within the granulations, and this process of ependymitis and choroiditis has even occluded the foramen of Magendie or the aqueduct of Sylvius.

The neurosurgeon must be wary when he encounters an arachnoid of milky aspect in looking for tuberculomas in the brain cortex, for this is a feature occurring in the brains of alcoholic patients or with cerebral tumors and may lead to a wrong diagnosis.

The microglia was observed to involve the tuberculoma.

SYMPTOMS

The time elapsed between onset of the first neurological sign and the date of admission to the Institute ranged from 10 days to nine years. Most of the patients came to the Institute because of a syndrome of intracranial hypertension. Figure 6 indicates the number of cases with such a syndrome and the localization of the

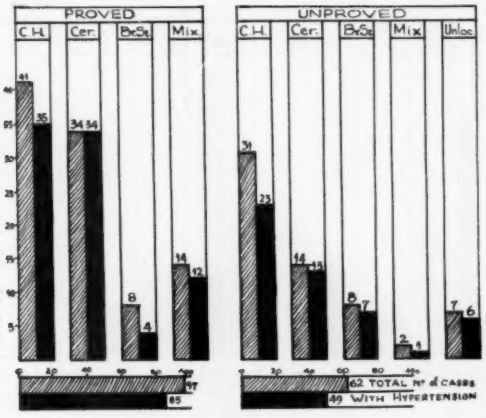

Fig. 6.—Incidence of intracranial hypertension.

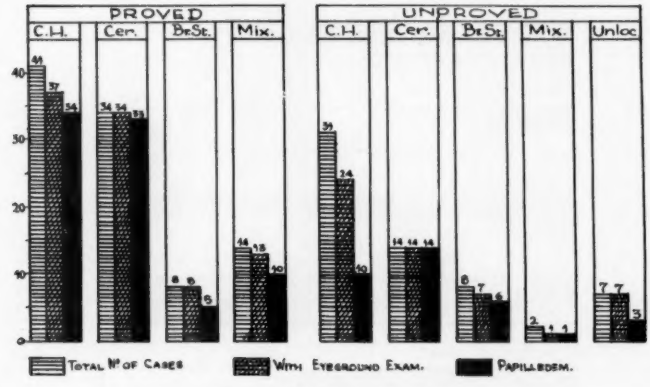

Fig. 7.—Incidence of papilledema.

lesion. Figures 7 and 8 show the incidence of the symptoms, with papilledema and increased intracranial pressure as revealed by the roentgenogram. Encephalographic and ventriculographic studies were performed in 84 cases (fig. 9). Figure 10 illustrates the distribution of roentgenographic findings. Arteriograms showed displacement and absence of vessels in the region of the tuberculoma.

We can confirm Orley's [14] statement (1949) that calcification of the tuberculoma is rare.

Electroencephalographic records of tuberculomas of the anterior fossa did not differ from those found with tumors, that is, slow waves with no other abnormality, as in the glioblastomas, or slow activity associated with focal sharp waves, as in the meningiomas, indicating a certain grade of cortical irritation. In other records a

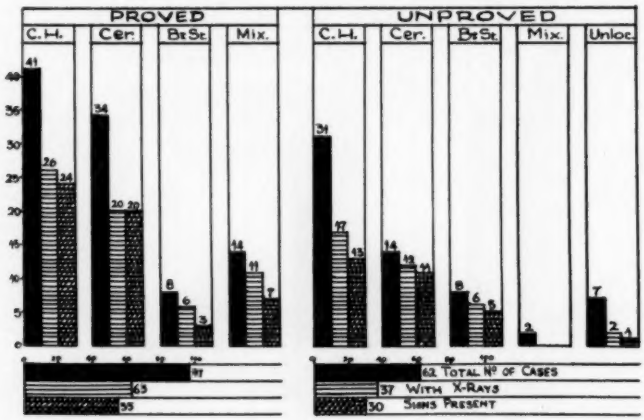

Fig. 8.—Incidence of signs of intracranial hypertension in simple roentgenograms.

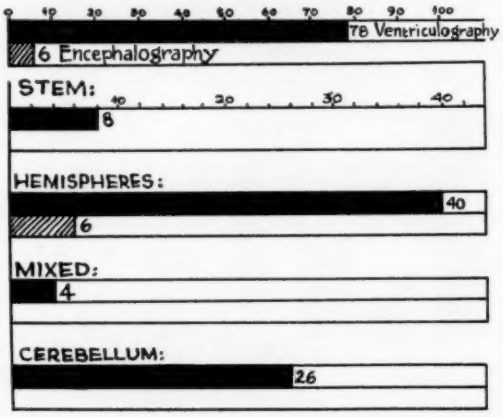

Fig. 9.—Incidence of ventriculography and encephalography in cases of tuberculoma.

decrease in the activity with slow waves and reversal phase, as in the astrocytomas, was registered. With tuberculomas of the posterior fossa, the electroencephalographic characteristics were similar to those recorded with tumors of the cerebellar cavity: slow waves with or without hypersynchronous activity, indicating acute hydrocephalus or spreading cerebral edema.

14. Orley, A.: Neuroradiology, Springfield, Ill., Charles C Thomas, Publisher, 1949.

DIAGNOSIS

In diagnosis, one must take into consideration, (1) existence of an intracranial tumor; (2) localization; (3) extension; (4) the tuberculous nature. In the analysis of each factor, we evaluate the following data:

Family history. Special importance is given to contact with tuberculous members of the family and to contact with open cases.

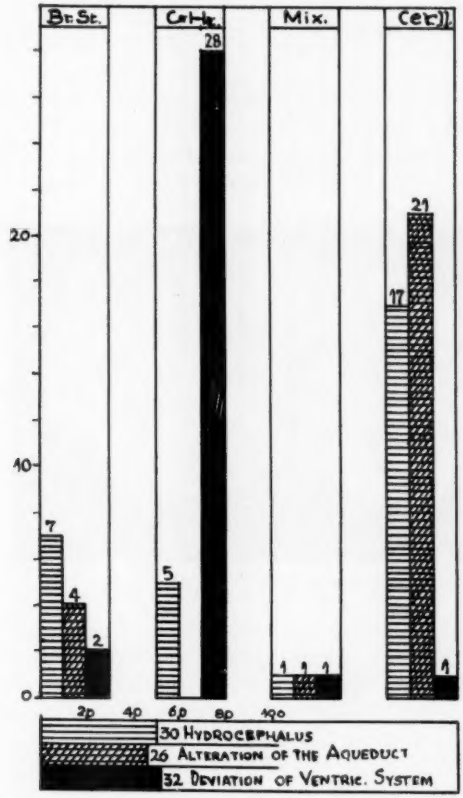

Fig. 10.—Results of ventriculographic and encephalographic examinations.

Personal history. (*a*) Race: Tuberculosis predominates among the mestizos and the aborigines because of their weaker biologic resistance.

(*b*) Age: Our statistics show that the disease is most frequent before the age of 30 years.

(*c*) Socioeconomic environment: Such factors as food, housing and type of work are significant.

Past or present history of tuberculosis. In children the symptoms subsequent to infection, producing allergy, should be noted.

Symptoms. Among the typical symptoms of intracranial hypertension, special emphasis is given to "headache," which, although it may occur frequently in tuberculous toxemia, is of chief significance in patients who show an abrupt change in their type of headache or in whom the headache appears as a new and persistent symptom in the course of a tuberculous infection. As careful an evaluation should be made of the headache as of the other symptoms of general or localized intracranial hypertension, for it is usual to blame any extracerebral tuberculosis more than the intracerebral type for these signs. The presence of papilledema and neurological disturbances and the evidence in the cranial roentgenogram are of decisive significance.

Physical examination. A general physical examination is indispensable. Careful search for foci of tuberculosis in the lungs or other organs is essential.

Neurological examination. The symptoms depend on the location of the tuberculoma, but it must be remembered that, owing to the serpiginous spread of this

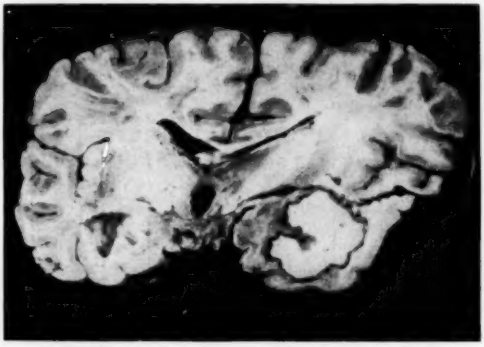

Fig. 11 (case 4924).—Serpiginous growth of a tuberculoma in the temporal lobe.

growth, the symptoms do not follow a set pattern. Sometimes the process infiltrates the tracts and nuclei without destroying them, producing no symptoms (fig. 11).

Roentgenological study. Owing to the epidemiological state in this country, calcification of tuberculoma is rare. Calcification does not mean cure of the lesion but probably indicates a halt in its course. Roentgenograms reveal only the signs of intracranial pressure.

Laboratory tests. Determination of the sedimentation rate, the Mantoux test in children before the age of 3 years, blood studies and examination of the spinal fluid are helpful.

Pathological study of the growth at operation. Histological diagnosis through vital staining with methylene blue by the Reid technic, especially with tuberculomas of the cerebellum, is very difficult if the Langhans cells are not present. We have mistaken pinealomas and isomorphous glioblastomas for this lesion.

Localization. We use air encephalography, ventriculography and arteriography, and electroencephalography is becoming more important.

TREATMENT

Until two years ago, surgical intervention was resorted to only to decrease the intracranial pressure, a decompression being used to relieve the patient from subsequent disturbances. Removal of the tuberculoma was rarely carried out. As shown in table 4, removal of the growth, before the use of streptomycin, was carried out in six cases, with survival in only one. Generally death was caused by tuberculous meningitis, which appeared three to four months after the operation. Little had been accomplished to better the depressing picture painted by von Bergmann [14a] (1899). The present day position in this respect has changed with the use of preoperative and postoperative treatment. The dangers of neurological complications, meningitis or a new focus, are greatly lessened, even if they have not disappeared.

In general, our surgical procedure is guided by the following considerations: (*a*) evaluation of the stage and curability of the pulmonary or nonpulmonary lesions; (*b*) general condition of the patient; (*c*) possible nontuberculous origin

TABLE 4.—*Type of Operations and Results*

	Hemispheres		Cerebellum		Brain Stem		Mixed		Total	
	Discharge	Death	Discharge	Death	Discharge	Death	Discharge	Death	Discharge	Death
Decompression with ventriculography...	20 (2) *	8	9 (1)	13	(1)	3	..	3	29 (7)	27
Decompression without ventriculography	2	1	4	4	..	..	..	2	6	7
Partial resection.....	1	2	1	..	..	..	..	1	2	3
Total resection.....	4 †	3 ‡	1 ‡	(1) ‡	..	..	..	1 ‡	5	4 (1)
Total with ventriculography.....	25 (2)	13	11 (1)	15 (1)	(1)	3	..	5	36 (7)	34 (1)
Total without ventriculography.....	2	1	4	4	..	..	..	2	6	7

* Numbers within the parenthesis refer to unverified tuberculomas.
† Treated with streptomycin.
‡ Without streptomycin.

of the intracranial malformation, in which case surgical exploration must be attempted; (*d*) possibility of total removal of the granuloma.

As may seen in figure 12, we refrained from operating in 67 cases of tuberculoma, in 22 of which the patient died, and in every case the lesion was disclosed at necropsy. Surgical treatment was attempted in 91 cases and, as indicated in table 4, most of the operations were confined to decompression following the ventriculographic procedure. During the last three years we have changed our conduct toward these patients. With regard to tuberculomas of the brain stem, we considered the Torkildsen technic [15] as the most proper. At present we employ to a larger extent the Stookey-Scarff technic [16] of opening the lamina terminalis for the drainage of the cerebrospinal fluid. There were cases in which opening of only the anterior wall of the lamina terminalis was followed by complete sealing of the opening in a month.

14a. von Bergmann, E.: Die chirurgische Behandlung von Hirnkrankheiten, ed. 3, Berlin, Hirschwald, 1899.

15. Torkildsen, A.: A New Palliative Operation in Cases of Inoperable Occlusion of the Sylvian Aqueduct, Acta chir. Scandinav. **82**:117-123, 1939.

16. Stookey, B., and Scarff, J. E.: Occlusion of Aqueduct of Sylvius by Neoplastic and Non-Neoplastic Processes, with Rational Surgical Treatment for Relief of Resultant Obstructive Hydrocephalus, Bull. Neurol. Inst. New York **5**:348-377, 1936.

Streptomycin was administered two or three days prior to operation (1 Gm. in 24 hours, divided into three doses of 0.33 Gm. each, or into two doses of 0.50 Gm. each). We have not given larger amounts than 80 to 100 Gm. of the drug. We have not found any cases of intolerance.

We have used paraaminosalicylic acid, 10 Gm. daily, in association with other drugs. In one case we employed a sulfonate compound—promin*; P,P'-diaminodiphenylsulfone-N,N'-didextrose sulfonate—in doses of 1 Gm. daily during four months. We have increased the doses until we now give 16 Gm. of paraaminosalicylic acid and 2 Gm. of promin.* The total dose of paraaminosolicylic acid is 1,000 to 2,000 Gm.

In table 5 is the résumé of the results obtained with streptomycin treatment up to December 1949, with a considerable follow-up observation. The patients treated

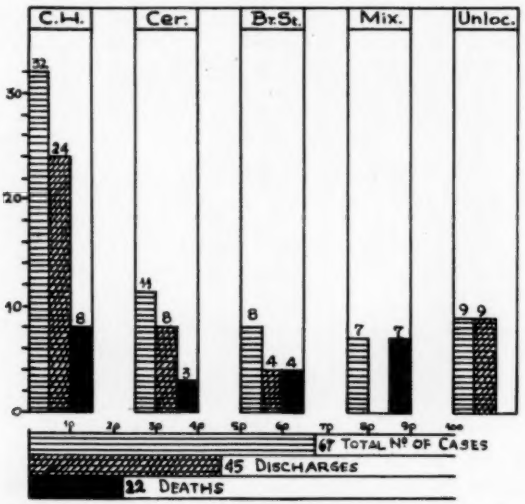

Fig. 12.—Mortality rate for tuberculomas not treated surgically.

in 1950 were not included. From the table one may see that the four patients with total excisions of the tuberculoma supplemented with medical treatment are in good condition, as are two patients with an ample decompression for a tuberculoma of the cerebellum and two with opening of the lamina terminalis for tuberculoma of the brain stem. The death of two patients was due to their very poor state and occurred soon after hospitalization.

Our position, then, regarding tuberculomas is as follows:

1. Administration of streptomycin together with paraaminosalicylic acid and promin* for several days before operation in the doses already mentioned.

2. In association with the medical treatment, the rest, suitable climate and special and extra feeding, appropriate to cases of tuberculosis.

3. Removal of all identified growths producing increased intracranial pressure by a technic that will not demand great excision of surrounding healthy tissue.

4. Decompression in cases of inoperable growths and drainage of the spinal fluid through the opening of the lamina terminalis and the posterior wall of the third ventricle, according to the Stookey-Scarff technic or the Torkildsen operation.

We must state that our surgical procedure is based on the fact that our experience with medical treatment is insufficient to allow us to guarantee a patient complete recovery with such treatment. However, in certain cases of tuberculosis, with early signs of increased intracranial pressure, in which there were no clear signs of localization and the diagnosis was tuberculous choroiditis or an early cortical process, medical treatment has proved beneficial.

PROGNOSIS

The prognosis depends on the clinical findings related to the tuberculosis, such as the stage of the disease, the general condition of the patient, the pulmonary state and extension of the foci, and on the pathological features, such as anatomic location, number of tuberculomas, spontaneous evolutive tendency, predominance of the mechanical manifestations of infection, pathological characteristics, adhesions and

TABLE 5.—*Summary of Data on Patients Treated with Streptomycin*

Case No.	Localization	Operation	Results
3820	Cerebellar hemisphere	Total resection	Alive
3838	Cerebral hemisphere	None	Dead
3909	Left frontal area	Total resection	Alive
4062	Cerebral hemisphere	None	Alive
4230	Multiple	Opening of lamina terminalis	Dead
4304	Cerebellum	Decompression	Alive
4338	Cerebellum	Total resection	Alive
4663	Cerebral hemisphere	Total resection	Alive
4669	Pons	Decompression	Alive
4747	Central nuclei	Opening of lamina terminalis	Alive

meningitis. These observations confirm our former statements. The employment of drugs has been of most valuable assistance in the treatment of these patients. It must be noted in this connection that the majority of tuberculomas of the central nervous system are single, thus increasing the surgical possibilities for lesions of this type, while with multiple tuberculoma, especially the mixed ones of bilateral location in the cortex or brain stem, operation is confined to decompression.

SUMMARY AND COMMENT

A series of 159 cases of tuberculomas of the central nervous system occurring at the Instituto de Neurocirurgia from Feb. 26, 1940 to Dec. 31, 1949 are reported; 97 of them were histologically verified.

Age, sex, family history, anergic diseases and standard of living are considered important factors in the pathogenesis of this lesion.

The diagnosis of cerebral tuberculoma can be made independently of pulmonary processes. Autopsies in 49 cases revealed six with no pulmonary signs.

A roentgenogram sometimes failed to reveal any process in the lungs; roentgenoscopy was of less assistance.

Pathological features of the growth are analyzed, as well as the changes in the microglia.

The characteristic symptom was the syndrome of increased intracranial pressure, which was an earlier and severer finding with tuberculomas of the posterior fossa and with multiple tuberculoma.

Diagnostic methods are described. Surgical decompression is commonly advised for relief of the increased intracranial pressure, and enucleation, if the growth is approachable and well circumscribed. Combined treatment with streptomycin and paraaminosalicylic acid and promin® (sodium P,P′-diaminodiphenylsulfone-N,N′-didextrose sulfonate) is of fundamental importance in the cure of the tuberculosis.

The cause of death was previously tuberculous meningitis, which appeared even after total removal of the tumor, or the development of extraneural tuberculous lesions. Although our experience is still insufficient, we can say that to date supplementation with the medical treatment described above has eliminated this cause of death.

Forty-two of 82 patients who underwent surgical treatment before the use of streptomycin are dead. Ten of these had partial or total resection of the growth; and of the six patients who underwent total removal, one survived. Of the 10 patients treated surgically and receiving streptomycin, two died. In one of the two patients operation was limited to opening of the lamina terminalis because of the presence of a large hydrocephalus and a poor general condition. The other patient was found to have multiple tuberculoma, and no definite treatment was attempted. Four patients had complete recovery with radical operation; two, with decompression, and two, with opening of the lamina terminalis.

In cases in which intracranial pressure was suspected, due to choroiditis or to a recent tuberculous process, with absence of localizing signs, medical treatment was carried out successfully.

ENCEPHALITIC FORM OF METASTATIC CARCINOMA

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AND
BERNARD J. ALPERS, M.D.
PHILADELPHIA

CARCINOMATOUS extension to the nervous system manifests itself in many fashions. Among these are solitary metastasis to the brain and multiple metastases of varying number and size. Less common, and not sufficiently recognized for either its pathological or its clinical features, is the encephalitic form of carcinomatous metastasis, which may closely simulate encephalitis of other types. It is to call attention to this form of metastatic carcinoma that the following cases are reported.

REPORT OF CASES

CASE 1.—J. A. (N.P. 42-154). *Bronchiogenic carcinoma in a man aged 55, with an organic mental syndrome; later appearance of hemiparesis, aphasia, cerebellar signs and convulsive movements. Diffuse carcinomatous infiltration of the meninges, brain, brain stem, cerebellum and spinal cord.*

History.—A white man aged 55 was first seen by one of us (B. J. A.) on July 26, 1942, at which time he stated that he was not as fit generally as he had been. His history was not very reliable, but his wife stated that he had begun to slow down 2½ years before examination. His gait became slow and careful, and, whereas he had formerly been a vigorous, outgoing person, he had to urge himself to meet people. In addition, he had become irritable and sarcastic. The difficulty with the gait persisted, but he never lost his equilibrium. For six months he had noticed a shaking of both hands and had cut himself several times while shaving. He had observed that his scalp was sensitive over the top of his head, and he had a feeling of congestion in the frontal portion with tightness over both eyes. For three weeks he had noticed difficulty in finding words, and he had to remind his secretary to tell him what he wanted to discuss when calling on the telephone. His ability to concentrate was poor; his speech had become less distinct, and he "mixed words," e. g., saying "potato" instead of "tomorrow." There was a past history of an operation for diverticulosis in November 1938, about 3½ years before examination. Two months prior to admission (May 1942) he fell from a bicycle and struck the left side of his head but seemed to have no definite injury. The positive neurological findings when he was first seen included pale, white optic nerve heads with blurred margins but no elevation of the disks. The retinal arteries were thin and moderately sclerotic. He had a coarse tremor of the lips; a fine tremor on extension of the fingers increased in the finger to nose test, especially on the right side, and the deep reflexes were overactive. The abdominal reflexes were absent. In addition, there were impairment of intellectual functions, dysarthria and slight expressive aphasia.

The aphasia increased, and the intellectual impairment became pronounced. There developed weakness of the lower half of the right side of the face and a tendency to veer to the right in walking. Cerebellar signs became pronounced. Two months before examination, his eyes deviated to the right, and he was unable to move them to the left. There later developed right hemiparesis, which became a complete right flaccid hemiplegia; his neck

From the Department of Neurology, Jefferson Medical College of Philadelphia.

became stiff, and he had a strong Kernig sign on the left side. The course was rapidly downhill, and a few days before death he exhibited partial continuous epilepsy of the left side of the face.

Lumbar puncture revealed initial pressure of 100 mm. of water. The fluid was clear and colorless. There were 21 lymphocytes per cubic millimeter; the protein content was 35 mg. per 100 cc.; the reaction to the Wassermann test was negative, and the colloidal gold curve was normal. The blood count and all blood studies, including determinations of the urea nitrogen, cholesterol and sugar and the sedimentation rate, gave normal results. Roentgenograms of the skull showed no evidence of increased intracranial pressure. The pineal body was calcified and not displaced. There was clouding of the frontal and ethmoidal sinuses. A roentgenogram of the chest was normal. An electroencephalogram showed poorly developed potentials in both frontal lobes, as well as low voltage sharp waves and occasional showers of low voltage 3 per second waves. A ventriculogram revealed nothing abnormal.

General Necropsy.—At first a diagnosis of abscess of the upper lobe of the right lung was made; but when metastatic carcinoma of the brain was reported, further study of the lung was undertaken, and the pathologist made the following note: "Tissues outside the lung do not show any primary tumor. Gross examination of the lung reveals no tumor mass; the bronchi are patent and not infiltrated as far as they are traceable. No discrete lesion is found anywhere except for the abscess and its adjacent area of chronic pneumonia in the upper lobe of the right lung. Microscopically, only portions of two of eight sections show the tumor, which is of an infrequent, but characteristic, type that arises in the periphery of the lung, spreads on alveolar walls and has been designated as 'carcinoma alveologenica diffusa' by Ewing and others, in spite of its bronchiogenic origin. The tumor in this case is small, much of it having probably been destroyed by the abscess it created. It is undoubtedly the source of the cerebral metastasis in the case reported, as the sarcomatoid appearance in metastases is common in many anaplastic bronchiogenic carcinomas."

Brain.—Gross Examination: The brain was large, weighing 1,560 Gm. The dura was of normal thickness. Under the dura on the left side was a recent hemorrhage, which was about 5 mm. thick except in a small area anteriorly, where it formed a nodular clot. The gyri of the cerebral hemispheres were swollen and edematous. Under the arachnoid over the left cerebral hemisphere was a thin film of hemorrhage, and small pools were seen over the right hemisphere. There was some prominence of the cerebellar tonsils, but no foraminal or incisural herniations. The medulla was rotated so that the reticular area on the right side seemed more prominent and fuller than that on the left. Over the anterior portion of the pons was a small cystlike body, which measured 3 by 2 cm. It was loosely adherent to the pia-arachnoid, from which it peeled away readily. It did not infiltrate the pontile structure. It had a thin, translucent membrane, which looked like arachnoid and contained a gelatinous structure.

Section of the brain revealed a moderate amount of edema. Nothing of note was evident grossly in the cerebral hemispheres except for a needle track in the left parietal lobe, produced in tapping the ventricles. This was surrounded by fresh hemorrhage. The ventricles were normal in size and shape. In the middle cerebellar peduncle on the left side was a small area in which there was breakdown of tissue; it had a loose, yellowish, vacuolated appearance. A similar, larger area was seen in the white matter of the left cerebellar hemisphere. This area was more sharply defined, had a yellowish, necrotic appearance and was hyperemic. A small grayish area was seen around the central canal of the lower end of the medulla.

Microscopic Examination: Sections were taken from the frontal, temporal, parietal and occipital lobes and from the cerebellum, basal ganglia, brain stem and spinal cord. These blocks were embedded in pyroxylin and stained with toluidine blue, Weil's modification of the Weigert stain and hematoxylin and eosin.

The leptomeninges over the cerebral hemispheres were moderately thickened with a fibrous proliferation. There was diffuse cellular infiltration, the cells being a mixture of carcinoma cells and phagocytes, most of which were plasma cells. The carcinoma cells were composed of a large nucleus with a heavy membrane, a few coarse chromatin structures and a round mass of granular, pale-staining cytoplasm. Mitoses were occasionally seen but were not overly abundant. However, amitotic cell divisions were common. The carcinoma cells were seen in the perivascular spaces dipping into the superficial layers of the cerebral cortex.

The meningeal blood vessels were thickened. There was intimal proliferation with scattered vacuoles in the intima, and frequently the adventitia was invaded by tumor cells.

The cortical blood vessels were also thickened, and many were surrounded by a ring of infiltrating cells, which was thicker about some than others. The cortical cytoarchitecture was fairly well preserved, but many of the ganglion cells were shrunken and dark staining. There was an increase in neuronophagia and satellitosis, and the microglia and oligodendroglia in the gray matter were increased. In the white matter, as in the gray matter, the infiltrating cells were loosely scattered, either taking a perivascular arrangement or, more commonly, being diffusely strewn through the tissue, with a tendency to become concentrated into con-

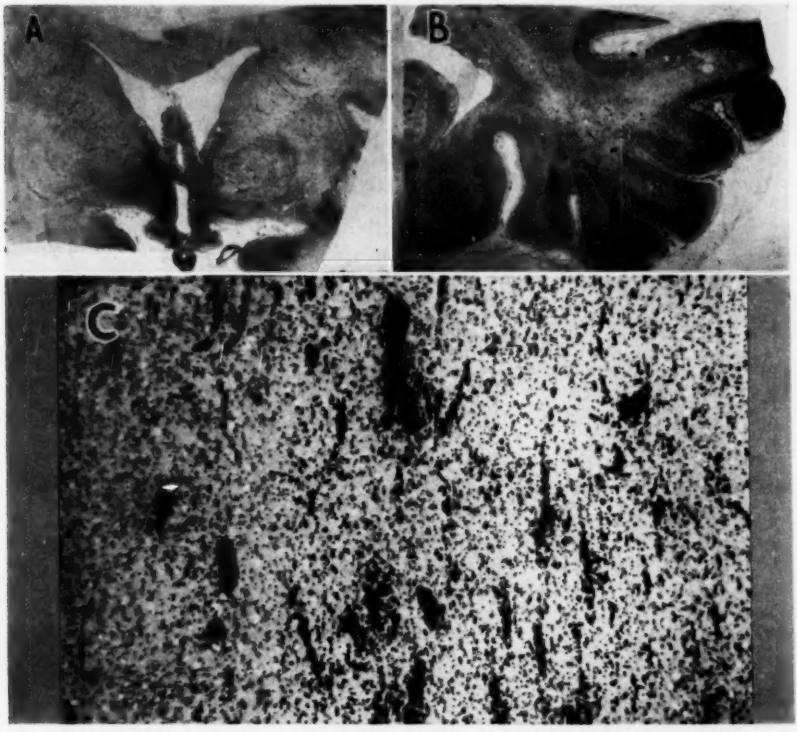

Fig. 1.—*A*, section at the level of the optic chiasm, showing the stria-like distribution of the carcinoma cells. Semigross Section; toluidine blue stain. *B*, section through temporal lobe, showing a similar distribution of cells, chiefly in the white matter. *C*, microscopic view of collections of carcinomatous cells, showing their typical arrangement.

densed foci at times. In some regions these cells appeared to have a stria-like distribution when the section was examined grossly (fig. 1). Oligodendrocytes and astrocytes were frequently intermingled with the cells. In the affected areas the Weigert stains revealed some loss of myelin.

The sections through the cerebellum revealed similar changes. There was a diffuse cellular infiltration, the cells again taking a perivascular arrangement, but streaking was widespread. Although all parts of the cerebellum were involved, the heaviest infiltration was seen in the white matter.

The basal ganglia were heavily infiltrated. This infiltration was particularly prominent in the region of the striate body, where striae of infiltrating cells accentuated the normal markings. Tumor cells were seen throughout the corpus callosum. The tegmentum of the pons and the colliculi were heavily infiltrated, as were the dorsal vagus nucleus and the nucleus ambiguus in the medulla. Cells were also spread diffusely through the rest of the reticular substance and the pontile nuclei. The nucleus of the hypoglossal nerve was infil-

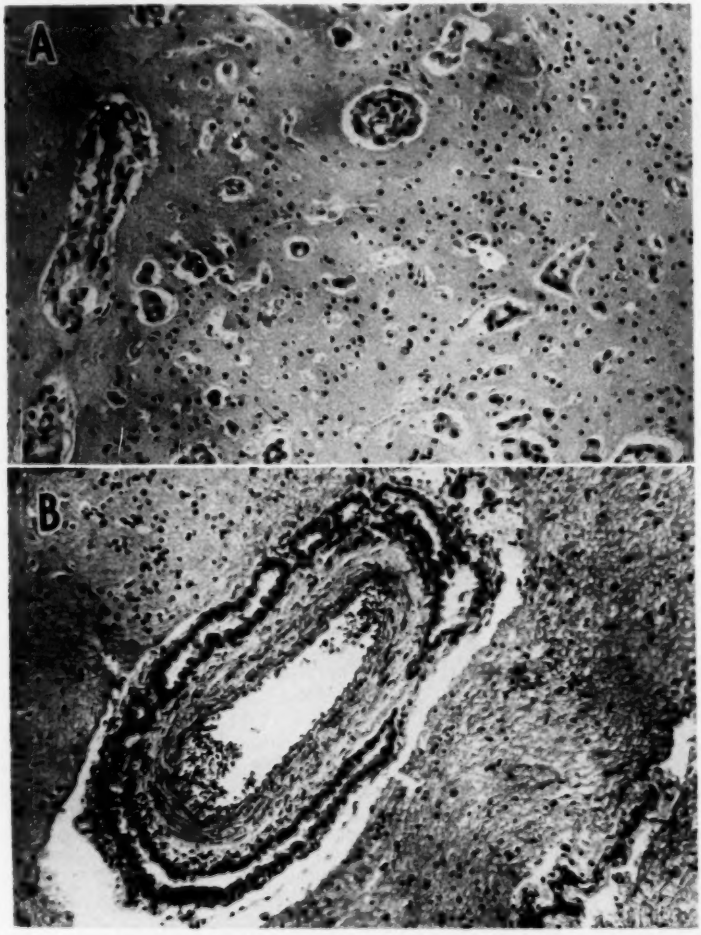

Fig. 2.—*A*, section at the junction of the gray and the white matter, showing predominant perivascular distribution of carcinoma cells. *B*, a larger blood vessel, showing the same perivascular arrangement, without spread to the surrounding tissue.

trated, the ganglion cells themselves being fairly well preserved, although many had loss of chromatin substance and eccentrically placed nuclei (fig. 2).

The meninges of the spinal cord were clear. The substance of the spinal cord, however, was diffusely infiltrated with cells, which were not arranged in any particular pattern but were more heavily scattered in the white matter. The anterior horns were infiltrated, but the ganglion cells were well preserved.

Summary.—The primary tumor in this case was a bronchiogenic carcinoma, associated with diffuse infiltration of carcinoma cells in all parts of the cerebrum. Sections of the frontal, motor, temporal, parietal and occipital areas showed infiltration, chiefly in the white matter, but also in the cortex. All parts of the brain stem were infiltrated, as well as the cerebellum. The cells were loosely scattered, took a perivascular arrangement or were packed in rather discrete nodules of varying size. The Weigert stain revealed loss of myelin in the affected areas.

CASE 2.—R. S. (J. H. 12554). *Syncopal attacks and headache for 10 years in a man aged 48, with convulsions and an organic mental syndrome for one month. Choked disks and nuchal rigidity but no localizing signs. Primary site not identified; diffuse carcinomatous infiltration of the meninges, both cerebral hemispheres and the brain stem.*

History.—A white man aged 48 was admitted to the service of Dr. Allison Price in the Jefferson Hospital on March 18, 1948, with the complaint of syncopal attacks for the past 10 years and convulsions for about one month. The history revealed intermittent headaches for 10 years, with persistent headaches in the occipital area for the past three weeks. For several months he had had tinnitus and questionable difficulty with language, which he described as "mixing my words." He had occasional momentary periods of diplopia. Five years before entrance to the hospital he had had an episode of unconsciousness, when he fell to the ground and struck his head. Two years prior to admission, while in bed, he had a sudden pain in the back of his neck, became pale and felt faint. This attack lasted about two hours and was followed by nausea. After this episode he had a sensation of unsteadiness and of falling backward. He noted that lifting or laughing caused weakness and black-outs. At such times his pulse became weak and he was cyanotic. All but two of the attacks occurred while he was in the erect position. The only aura he could describe was the feeling of being "motionless" and of being about to lose consciousness. He had shown signs of irritability but no memory changes.

For 12 years he had had intermittent pains in the abdomen, lasting three to four days and then disappearing for several months. Six years prior to admission he had pains in the knees. Roentgenograms revealed fracture of a vertebra, but there was no history of trauma. He was said to have been kicked in the head by a horse at the age of 15.

Physical examination revealed a moderately nourished man who complained of pain in the occipital region. The blood pressure was 150/110 in the left arm and 140/110 in the right arm. There was nuchal rigidity. The chest was clear and the heart normal. Tenderness was elicited in both upper and lower quadrants of the abdomen; this was difficult to evaluate. The prostate was enlarged, and there were external hemorrhoids. The rest of the physical examination revealed nothing abnormal.

A neurological consultant observed the following abnormal signs: bilateral papilledema, the right disk being greater than the left; hemorrhages in the right eye, and nuchal rigidity without Kernig's sign. There were no focal cerebral signs. The patient was thought to have a brain tumor, possibly in the temporal lobe. A roentgenogram of the skull revealed nothing abnormal. A 16 lead electroencephalogram showed well developed 10 per second activity with a few scattered spikes in the midparietal region, but there was no definite activity to indicate a focal cerebral lesion. Examination of the spinal fluid revealed a total protein of 48 mg. per 100 cc., no cells and a negative Wassermann reaction. The blood count showed 16,700 white blood cells; 75 per cent neutrophils, of which 65 per cent were segmented and 10 per cent nonsegmented forms; 13 per cent lymphocytes, and 12 per cent eosinophils. The urine was normal; the blood urea nitrogen measured 20 mg., and the creatinine 20 mg., per 100 cc.

Eight days after his admission a ventriculographic study was performed and revealed very slight displacement of the ventricular system to the left and narrowing of the right temporal horn. The patient was then returned to the operating room, and a bone flap was turned down in the right temporoparietal region. There was no obvious increase in intracranial pressure. The cortical arteries were arteriosclerotic. About one third of the way up

from the sylvian fissure, and approximately in the motor convolution, was a tiny red nodule, about 2 mm. in diameter. It was excised, together with the underlying cortex. The area of the brain over the temporal tip of the motor cortex appeared soft. No obvious lesion was disclosed. Examination of the small nodule revealed that it was metastatic carcinoma. The day after operation the patient became extremely restless and made many attempts to get out of bed. He mumbled and was out of contact with the environment. The next day the pulse and respiration rates and the temperature rose; the blood pressure dropped, and two days later the patient died.

Necropsy revealed acute suppurative bronchopneumonia, with miliary abscesses and squamous metaplasia of the bronchiolar epithelium; severe atherosclerosis of the coronary arteries; moderate arterial nephrosclerosis; lipid depletion of the adrenal glands; fatty changes in the liver, and nodular hyperplasia in the prostate.

Brain.—Gross Examination: The brain measured 17.5 by 11 by 10 cm. All the convolutions were flattened, particularly those over the vertex of each hemisphere. There was slight notching of the hippocampal gyrus. The meninges were slightly thickened and opaque. In the right frontal lobe just above the sylvian fissure, at the foot of the precentral convolution,

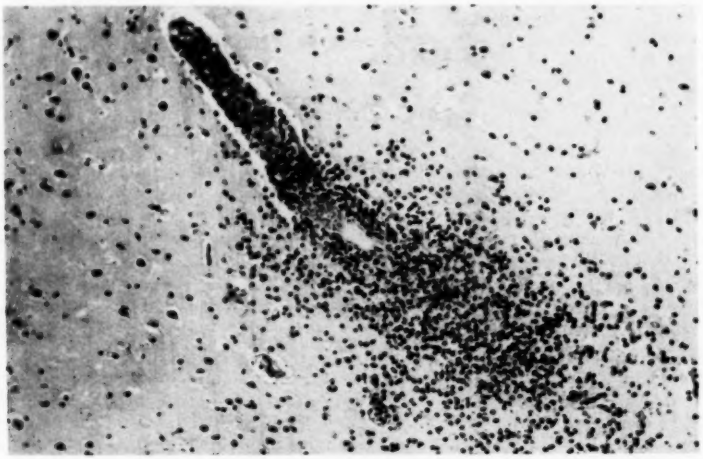

Fig. 3.—Reaction of polymorphonuclear leukocytes in the cortex to meningeal infiltration with carcinoma cells.

was an area of laceration. Coronal sections of the cerebrum showed that the white matter of the left temporal lobe was unusually pale and shiny, while the gray matter was not as prominent as normal. The white matter was everywhere edematous. In the corpus callosum on the right side just anterior to the splenium were two discrete hemorrhagic lesions, each about 4 mm. in diameter. The site of the surgical incision extended through the island of Reil to the external capsule at the level of the appearance of the globus pallidus; the edges of the incision were soft, necrotic and hemorrhagic. There was normal dilatation of the anterior horns but no ventricular displacement. No tumor masses were seen on gross examination.

Microscopic Examination: Sections were taken from all lobes of the cerebral hemispheres, the basal ganglia, the cerebellum and the brain stem. These blocks were embedded in paraffin and sections studied with toluidine blue and hematoxylin-eosin stains.

The leptomeninges overlying the cerebral hemispheres were normal except for occasional small discrete collections of infiltrating cells. These cells invaded the cortex via the perivascular pathways. The meningeal blood vessels had undergone engorgement and dilatation, and fresh subarachnoid blood was seen. The perivascular and pericellular spaces in

the cortex were dilated, particularly in the temporal lobe, but the ganglion cells and the cytoarchitecture were well preserved. Occasionally in the various sections of the cortex studied there were small discrete collections of cells, in both the gray and the white matter. These cells were composed of large vesicular nuclei with scattered, coarse chromatin material and a stout nuclear membrane, in a round or polygonal mass of finely granular cytoplasm. The cells were arranged in poorly defined lobular formation. Many mitotic figures were seen. Occasionally amitotic division was observed. One of the blood vessels near a nodule of cells had a perivascular cuff of polymorphonuclear leukocytes and lymphocytes (fig. 3). In the gray matter there was cuffing of blood vessels by the infiltrating cells. A similar collection of cells was seen in the pons at the edge of the ependyma lining the fourth ventricle. Scattered through the tegmentum of the pons were similar small collections of cells, all within the parenchyma. No perivascular cuffings were seen. No infiltrations were noted in the cerebellum. The inferior medullary velum contained a small discrete collection of cells, which did not invade the choroid plexus of the fourth ventricle. The meninges at the base of the medulla contained a very small collection of infiltrating cells. The ganglion cells of the hypoglossal nerves were pale and had lost much of their chromatin substance, but the hypoglossal nuclei were not invaded by cells. The inferior olivary nuclei were well preserved.

Summary.—The primary source of the metastases was not proved in this case, but there was invasion of the cerebral hemisphere and the brain stem by small discrete, scattered nodules in the meninges and in the gray and white matter. The nodules in the cerebral substance were almost entirely within the tissue itself and were not perivascular. The pons and medulla were involved in the region of the fourth ventricle. There was some perivascular cuffing with polymorphonuclear leukocytes and lymphocytes near the nodules in the cortex.

CASE 3.—A. G. (J. H. 11334). *Convulsions, left hemiplegia and an organic mental syndrome in a miner aged 47, who was known to have had tuberculosis. Bronchiogenic carcinoma with diffuse involvement of the meninges, cerebral hemispheres, brain stem and cerebellum was found.*

History.—A white man aged 47 entered the Jefferson Hospital on Jan. 31, 1949, because of disorientation, confusion and seizures involving the left side. He had been a miner for approximately 20 years, and three years prior to his admission, when he was attempting to obtain employment in the mines, a routine roentgenogram of the chest had revealed evidence of pulmonary tuberculosis. He then spent eight months in a sanatorium, where he was treated with bed rest. His sputum became negative for acid-fast bacilli, and he was discharged. He worked at odd jobs for the next year, but a year before admission to the Jefferson Hospital he was readmitted to the sanatorium with tubercle bacilli in the sputum and roentgenologic evidence of an area of atelectasis in the upper lobe of the left lung.

He had his first generalized convulsion 15 months before admission. Similar attacks developed in subsequent months. On Jan. 2, 1949, 29 days before admission to the hospital, he was sent to the tuberculosis division of the Jefferson Hospital, where his sputum was found to be free from tubercle bacilli and an area of homogeneous increased density was noted in the upper lobe of the left lung. Tomographic studies revealed no evidence of cavities in this area.

Bronchoscopic study revealed rigidity and compression stenosis of the main bronchus of the left lung, clinically interpreted as possible carcinoma of the left lung. The bronchial secretion was negative for carcinoma cells. Spinal puncture showed an initial pressure of 175 mm. of water; the fluid was clear and colorless, with 25 mg. of glucose, 739 mg. of chloride and 304 mg. of protein, per 100 cc., and less than 2 cells per cubic millimeter.

The patient became disoriented and confused; paralysis of the left upper and lower limbs developed, and he was transferred to the neurology service for further investigation. On admission he was confused and unable to tell a coherent story but complained of having had headache on the right side for some time. Neurological examination revealed pronounced weakness of the left arm and leg and some weakness of the right leg; constant exten-

sor movements of the left hand and left great toe; loss of position sense in the left thumb and left great toe; dyssynergia of the left arm; pronounced nuchal stiffness, and a bilateral Kernig sign.

Routine roentgenograms of the skull showed thinning of the dorsum sellae, with generalized decalcification of the bones of the skull, a condition suggesting increased intracranial pres-

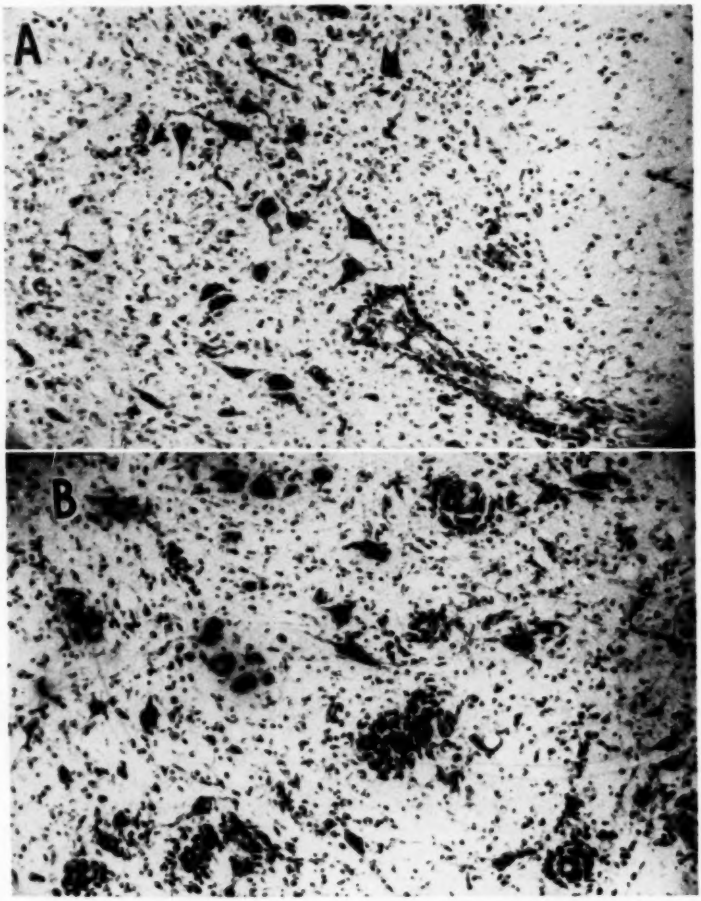

Fig. 4.—*A*, section of spinal cord with invasion of the perivascular spaces and attenuation of ganglion cells. *B*, view of hypoglossal nucleus, showing varied distribution of the carcinoma cells, some taking a perivascular arrangement, others collected in tiny discrete nodules and some scattered throughout the tissue.

sure. A pneumoencephalogram showed good filling of the ventricular system without dilatation, shift or deformity. A 16 lead electroencephalogram showed numerous spiking discharges, which were bilateral, sometimes in synchrony and sometimes not. There were two distinct foci, one in the left frontomedial and the other in the right occipitomedial area. Two sub-

sequent studies of the spinal fluid revealed the total protein to be 188 mg. per 100 cc. on one occasion and 256 mg. on another, without other findings of significance. Seizures developed on the left side and later became generalized. These could not be controlled with the usual anticonvulsant drugs, and on March 15, 1949 the patient died. The temperature was normal until three days before he died when it rose to 101 F. and remained elevated until his death.

Necropsy revealed bronchiogenic adenocarcinoma, intermediate grade, with alveolar cell distribution and metastases to the pleura, hilar lymph nodes and right adrenal gland. There were bilateral bronchiectasis, anthrosilicosis, emphysema and fibrocaseous tuberculosis. There was also tuberculosis of the vesicoureteral orifices.

Brain.—Gross Examination: The brain weighed 1,070 Gm. and appeared heavy and edematous. The sulci were obliterated, and the entire dorsolateral surface was covered with a thick, creamy exudate, which was also present in the sylvian fissure and seemed to be much more prominent over the basilar surface of the brain, especially the orbital gyri and the temporal lobe bilaterally. The exudate was also present over both hemispheres of the cerebellum. There was no indication of arteriosclerosis. The leptomeninges at the base of the brain were thickened. The vessels over the lateral surface of the brain were congested and prominent. Coronal sections of the cerebrum showed thickening of the leptomeninges, edema of the gyri and obliteration of the sulci. The ventricular system was normal. No tumor masses were seen.

Microscopic Examination: Sections were taken from all lobes of the cerebral hemispheres, the cerebellum and the brain stem. These were embedded in pyroxylin and stained with toluidine blue, Weil's modification of the Weigert stain and hematoxylin and eosin.

The leptomeninges overlying the cerebral hemispheres had undergone fibrous thickening. There was intimal proliferation in the meningeal blood vessels. In some sections, especially those of the parietal, temporal and occipital lobes, the meninges were heavily infiltrated with cells arranged in lobular formation, either scattered diffusely throughout portions of the meninges or collected in small discrete nodules. The cells, which were columnar, were composed of an elongated, large vesicular nucleus, containing sparse coarse chromatin material, in a finely granular cytoplasm. Many mitotic figures were seen. Frequently the cells in the meninges were seen extending into the cerebral tissue, usually in the perivascular spaces but also by direct extension. In some sections small collections of these cells were seen scattered in the gray and white matter, the predilection being for the gray matter. The cytoarchitecture was well preserved except where distorted by the infiltrating cells. In these regions there was an increase in oligodendroglial and microglial cells. Most of the ganglion cells were attenuated and pyknotic. In the white matter the infiltrating cells were usually perivascular and without surrounding cellular reaction (fig. 4). The leptomeninges overlying the cerebellum were also heavily infiltrated with cells in some portions, while other areas were clear. Direct extension of cells into the cortex could be seen. In addition, there were discrete perivascular collections of cells unrelated to meningeal extensions in all layers of the cerebellum. In the medulla, several heavy perivascular infiltrations were present in both restiform bodies. The remainder of the brain stem was normal.

Summary.—In this case, in which pulmonary tuberculosis was originally suspected a large bronchiogenic carcinoma with extension into the leptomeninges overlying both cerebral hemispheres and the cerebellum was found. Direct invasion and extension into the perivascular spaces were seen, in addition to discrete perivascular collections of carcinoma cells in the gray and white matter of the cerebral hemispheres, all layers of the cerebellum and the restiform bodies of the medulla.

CASE 4.—R. F. (J. H. 14249). *Severe headaches, increased intracranial pressure, convulsions and an organic mental syndrome in a woman aged 31, with carcinoma of the lung. Diffuse infiltration of the meninges, cerebral hemispheres and cerebellum.*

History.—A white woman aged 31 was admitted to the service of Dr. Rudolph Jaeger in the Jefferson Hospital on May 12, 1946 for diagnosis and treatment.

The history revealed that 15 months previously the patient had had onset of severe generalized headaches. She also had nausea and vomiting, not projectile in character. She

was studied in another hospital and found to have bilateral papilledema and partial sensory aphasia. Later a paralysis of the sixth nerve developed, and she had had a generalized convulsion. A ventriculogram revealed a normally outlined ventricular system, but, because of a greatly increased intracranial pressure, a decompression was performed in the right subtemporal area. After this she did well, until signs of increased intracranial pressure, including severe headaches and bouts of vomiting, again developed. Another ventriculogram revealed nothing abnormal. The intracranial pressure increased, however; the patient became unconscious, and the right temporoparietal area was explored but no tumor was found. Postoperatively the patient did fairly well but had several convulsions, which were controlled with diphenylhydantoin sodium and phenobarbital. On her discharge, the physical findings included early secondary optic nerve atrophy of both eyes, a dulled sensorium, but absence of neurological signs, and a spinal fluid pressure of 90 to 100 mm. of water. The patient returned home, and the defect in the cranium became increasingly obvious, so that she sought further treatment and was admitted to the Jefferson Hospital.

Examination revealed herniation through the site of the subtemporal decompression; loss of sensation and power in the left arm and, to a less extent, in the leg; yellowish white pallor of the right disk, and pallor of the left disk. An eight lead electroencephalogram was reported as follows: "The record contains slow high voltage waves of about ½ second frequency over both hemispheres, especially the motor and parietal regions. These are somewhat more prominent on the right. There is no out-of-phase activity. This record is suggestive of a diffuse process." A ventriculogram revealed an unobstructed, but dilated, ventricular system as far as the outlet of the fourth ventricle. A craniectomy with exploration of the posterior fossa was performed, but a tumor was not found. Generalized seizures developed after operation. Several aspirations of yellow fluid were made from the incision, and repeated lumbar punctures revealed an initial pressure of 120 to 180 mm. of water with xanthrochromic fluid. The patient continued to have seizures and died about three months after operation.

Necropsy revealed pleural effusion on the right side and carcinoma of the lung of alveolar distribution, with metastases to the lymph nodes, trachea and kidney. There were pulmonary congestion and edema and a tubo-ovarian cyst on the right side.

Brain.—Gross Examination: The brain weighed 1,190 Gm. On the posteromedial aspect of the right cerebellar hemisphere was a laceration of cortex measuring 1.5 by 2 cm., the edges of which were soft and necrotic. The meninges over the vertex, where present, were opaque. The convolutions were flattened over both cerebral hemispheres. In the left occipital lobe there was a small fungus of cerebral cortex, extending out 7 mm., at the site of trephination. Coronal sections of the cerebrum revealed five scattered red-orange areas, poorly demarcated and measuring approximately 2 mm. in diameter, within the white matter of the left hemisphere. Cross sections of the brain stem and cerebellum revealed no gross lesions.

Microscopic Examination: Sections were taken from the temporal, parietal and occipital lobes, the basal ganglia, the small fungus of cerebral cortex and the cerebellum.

The leptomeninges overlying the cerebral hemispheres were irregularly infiltrated with cells. In some sections the infiltrations were heavy, with discrete collections in the sulci; in others the meninges were sparsely and diffusely invaded. The cells were mostly in nodular formation and were composed of large vesicular nuclei with stout nuclear membranes, containing chromatin granules, in columnar or oval masses of finely granular cytoplasm. Many mitotic figures were present. These cells extended directly into the cortex or invaded the perivascular spaces. There were, in addition, separate small collections of cells, mostly perivascular, in both the gray and the white matter of the cerebral hemispheres. In the regions where the tumor cells were present the architecture was distorted, but there was very little cellular reaction. Most of the ganglion cells were dark and shrunken, with an increase in satellitosis and neuronophagia. In sections through the corpus striatum several small perivascular collections of carcinoma cells were seen in the putamen. The meninges overlying the cerebellum were diffusely, but sparsely, infiltrated with carcinoma cells. At one edge of the dentate nucleus were several small blood vessels cuffed with infiltrating cells. There was also a small area of softening at one edge of the cerebellum, where the normal architecture was replaced by compound granular corpuscles.

Summary.—In this case of bronchiogenic carcinoma the meninges overlying the cerebral hemispheres and cerebellum were diffusely infiltrated with carcinoma cells. Perivascular infiltrations were also seen in the gray and white matter of the cerebral hemispheres, in the putamen and in the dentate nucleus of the cerebellum.

COMMENT

Clinical Features.—Metastatic carcinoma of the brain may manifest itself in an encephalitic form—encephalitic in the sense that it is diffuse, scattered, unassociated with tumor formation and infiltrating both the parenchyma and the perivascular spaces, as well as the meninges. No inflammatory reaction is involved; hence, the term encephalitis is inaccurate. On the other hand, it is difficult to find a completely satisfactory term to describe the form of metastatic carcinoma exemplified by the reported cases. The term encephalopathy avoids the criticism engendered by the term encephalitis, but it is inaccurate in the sense that any extension of carcinoma to the brain may be regarded as an encephalopathy. The term "diffuse" has similar shortcomings. The problem of nomenclature has troubled all those who have reported cases of this lesion. Hassin [1] described the condition as a "combination of focal and diffuse (encephalitic) lesions"; Globus, in a discussion of Weinberger's case,[2] as miliary carcinomas or diffuse encephalopathies, and Cornwall [3] as "metastatic meningoencephalitic carcinomatosis without tumefaction." If it is understood that the term carcinomatous encephalitis is applied to this form of metastatic carcinoma in a special sense, there appears to be no harm in its use; and it conveys better than any other term the type of spread represented by these cases.

The incidence of the encephalitic form of metastatic carcinoma is low. Of 106 pathologically verified cases of metastatic carcinoma in our laboratory, only the four cases reported represent pure forms of the encephalitic variety, an incidence of 3.8 per cent. Of 57 cases reported by Globus and Meltzer,[4] five were of this type. King and Ford [5] report one such case among 27 cases of pathologically verified carcinoma of the lung.

The clinical picture associated with carcinomatous encephalitis has no distinctive features. The process is diffuse, involving the brain or the brain stem or both. It is afebrile and develops in the presence of known carcinoma or in cases in which the latter is not suspected. It should always be suspected in middle-aged or older patients with what appears to be an encephalitic process of undetermined origin. In the four cases reported, all the patients had convulsions, three had an organic mental syndrome and three had hemiparesis. In a process which is capable of wide or limited spread to any part of the brain or the brain stem, it is obviously

1. Hassin, G. B.: Histopathology of Carcinoma of the Cerebral Meninges, Arch. Neurol. & Psychiat. **1**:705 (June) 1919.

2. Weinberger, L.: Miliary Metastatic Carcinoma of the Brain and Meninges (Case Presentation in Clinical Neuropathological Conference), J. Mt. Sinai Hosp. **4**:383 (Dec.) 1937.

3. Cornwall, L. H.: Metastatic Meningo-Encephalic Carcinomatosis Without Tumefaction, Arch. Neurol. & Psychiat. **17**:466 (April) 1927.

4. Globus, J. H., and Meltzer, T.: Metastatic Tumors of the Brain, Arch. Neurol. & Psychiat. **48**:163 (Aug.) 1942.

5. King, A., and Ford, F.: A Clinical and Anatomical Study of Neurological Conditions Resulting from Metastases in the Central Nervous System Due to Carcinoma of the Lung: Review of 100 Cases, Bull. Johns Hopkins Hosp. **70**:124 (Feb.) 1942.

impossible to describe symptoms common to all cases. In two of the four cases reported, choked disk was present, leading to the diagnosis of brain tumor. In neither instance were localizing signs found.

Pathological Features.—Gross inspection of the brain reveals nothing of significance. No tumors are visible to the naked eye. The brain is often edematous. The meninges may be cloudy and thickened locally or diffusely over the hemispheres and brain stem. Areas of hyperemia or linear streaks of engorged vessels may mark areas of heavy infiltration with tumor cells.

The meninges are frequently affected in the encephalitic form of metastatic carcinoma. They were invaded in all four of the cases here recorded, as well as in most of the cases previously reported. In three of the five cases described by Globus and Meltzer [4] microscopic study revealed carcinoma cells in the leptomeninges. Uspensky [6] noted metastatic cells in the pia-arachnoid of both the brain and the spinal cord. In Cornwall's case,[3] the leptomeninges were grossly thickened and microscopic study showed infiltration with carcinoma cells. In Weinberger's case [2] the meninges were also everywhere thickly infiltrated. In our case 3 the meninges were so heavily invaded that the brain appeared to be covered with a creamy exudate.

Any part of the brain or brain stem may be invaded by the process. In case 1 the extension was widespread and diffuse, involving the cerebrum, cerebellum and all parts of the brain stem. In case 2 the cerebral hemispheres were largely affected, together with the pons and medulla. In case 3 the cerebrum was diffusely involved, only the inferior cerebellar peduncles being affected in the brain stem. In case 4 the cerebrum, putamen and dentate nucleus of the cerebellum were invaded. In the cases described by Globus and Meltzer [4] the distribution was "of the character of a diffuse infiltration," specific areas not being mentioned. In the case of Uspensky [6] the spread included the cerebral hemispheres, the corpora striata, the midbrain, the cerebellum and the spinal cord. Cornwall observed carcinoma cells in all portions of the cerebral cortex, the brain stem and the cerebellum, with the heaviest infiltration in the midbrain. In the case cited by King and Ford [5] the entire brain, pineal body and hypophysis were infiltrated. Lewis [7] found the extension including all lobes of the cerebrum and the basal ganglia, brain stem, cerebellum and choroid plexus. It can be seen from this survey that the process extends in unpredictable fashion but that in all instances the cerebral hemispheres are involved in greater or less degree and the meninges are almost always invaded by the process.

In cases of the type described no large nodule or tumor formation is visible to the naked eye. The process becomes visible under the microscope. The meninges may be infiltrated diffusely or locally, heavily or lightly. The brain tissue may reveal direct extension of the carcinoma cells into the parenchyma, associated with perivascular infiltration of the cells, or there may be perivascular infiltration only. The ganglion cells reveal no specific changes, but loss and disease of the ganglion cells are noted in areas which are heavily infiltrated with carcinoma cells. The spinal cord may be involved precisely in the same fashion as the brain.

6. Uspensky, E.: On Diffuse Carcinomatous Metastases in the Nervous System, J. Neuropath. & Exper. Neurol. **2**:103 (April) 1943.

7. Lewis, N. D. C.: An Unusual Manifestation of Metastatic Miliary Carcinomatosis of the Central Nervous System, Am. J. Psychiat. **5**:171 (Oct.) 1925.

CONCLUSIONS

The term carcinomatous encephalitis is proposed to describe a diffuse spread of carcinomatous cells in the brain, including the meninges, parenchyma and perivascular spaces, without true nodule formation. Four such cases are reported. Clinically the cases varied considerably; but all four patients had signs of meningeal irritation, all had convulsions, three of the four had an organic mental syndrome and three of the four had hemipareses. Pathologically, in all cases there was infiltration of the brain and meninges, with carcinoma cells strewn throughout the substance of the brain, collected in tiny discrete nodules or located in the perivascular spaces. In three of the four cases the primary source was in the lung; in the fourth the primary site was not determined. The incidence of this condition among all metastatic carcinomas seen in our laboratory is 3.8 per cent. It should always be suspected in middle-aged or older patients with what appears to be an encephalitic process of undetermined origin.

EFFECTS OF DECAMETHONIUM BROMIDE (C 10) AND *d*-TUBOCURARINE ON ELECTROCONVULSIONS

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THE RELAXING effect of subparalyzing doses of *d*-tubocurarine chloride is sufficient to render electric convulsion therapy almost without complications. When this drug is used judiciously, there are, again, almost no complications due to individual sensitivity or idiosyncrasy to the drug. However, when the presence of severe cardiovascular, osseous or other organic disease makes it desirable to obtain maximum curarization and modification of the electric fit, *d*-tubocurarine chloride, in the opinion of many, may fall short of being an ideal drug. Its use in doses sufficiently high to achieve a maximum relaxing effect is at times accompanied with an untoward degree of apprehension and respiratory distress, post-treatment apnea, or bronchospasm from the histamine-like action of the drug. That this apprehension and respiratory discomfort are of importance is indicated by the fact that, aside from the fear of the treatment itself, this distress, once it is experienced, constitutes the patient's principal objection to the treatment.

It is the purpose of this report to determine whether a maximal degree of paralysis and softening of the electrically induced convulsions can be more easily obtained without respiratory distress with the newer synthetic neuromuscular blocking agent decamethylene-1, 10-bistrimethylammonium dibromide (decamethonium bromide [C 10])[1] than with *d*-tubocurarine chloride. In those instances in which a maximum effect can be obtained with both drugs, the effective doses may be compared to determine whether there is any correlation in the tolerance to the two drugs and an equipotent dosage may be established.

Since the original reports[2] concerning the neuromuscular blocking properties of bistrimethylammonium decane diiodide (C 10), several communications have

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1. Syncurine, a brand of decamethonium bromide, is marketed by Burroughs Wellcome & Company, Inc., who supplied the drug for this study. It contains 1 mg. of decamethonium bromide per cubic centimeter.

2. Paton, W. D. M., and Zaimis, E. J.: Curare-Like Action of Polymethylene *Bis*-Quaternary Ammonium Salts, Nature, London **161**:718 (May 8) 1948; Clinical Potentialities of Certain Bisquaternary Salts Causing Neuromuscular and Ganglionic Block, ibid. **162**:810 (Nov. 20) 1948. Organe, G.; Paton, W. D. M., and Zaimis, E. J.: Preliminary Trials of Bistrimethylammonium Decane and Pentane Diiodide (C10 and C5) in Man, Lancet **1**:21 (Jan. 1) 1949.

dealt with the use of this agent in electric convulsion therapy.[3] In these studies the action of the drug was compared with that of curare, and conclusions were drawn as to the comparable doses of these two drugs. In summary, the following observations were reported:

The "curarization" effects of decamethonium bromide and *d*-tubocurarine chloride were found indistinguishable, except that most investigators were convinced that the respiratory apparatus was relatively spared with decamethonium bromide. Others [3c] reported less involvement of pharyngeal, laryngeal and facial muscles. There was uniform agreement that the effects of decamethonium bromide passed off more quickly than those of *d*-tubocurarine chloride and that the occasional histamine-like effects produced by *d*-tubocurarine chloride were absent with decamethonium bromide. No effective antidote, such as neostigmine, is known for decamethonium bromide; but, judging from these reports and from Davies' [4] experience in administering 973 treatments to 125 patients, there is little indication that an antidote is needed with the doses used in electric convulsion therapy.

In two of these studies [3b, c] the effective dose of decamethonium bromide was found to be one-fourth that of *d*-tubocurarine chloride. In terms of the actual dose, the therapeutic doses of *d*-tubocurarine chloride and decamethonium bromide were determined by Hobson and Prescott [5] as 0.3 and 0.08 mg. per kilogram of body weight, respectively. In another study, by Grob and associates,[3c] comparable degrees of complete, or almost complete, peripheral relaxation were obtained with 2.0 to 2.75 mg. of decamethonium bromide and 9.0 to 12.0 mg. of *d*-tubocurarine chloride. In this report, and in that of Davies and Lewis,[3a] the dose of decamethonium bromide was found not to depend on body weight. There is no mention in any of these reports of the presence of any correlation between the tolerances to the two drugs.

The criteria for adequate "curarization" on which to base comparisons for the establishment of an equipotent dosage varied in these studies. The standards used consisted of various degrees of modification of the electric fit up to "much reduction or total abolition of visible clonic movements in trunk and limbs" [3a] and various shades of paralysis up to complete, or nearly complete, peripheral relaxation.[3c]

PROCEDURE

Decamethonium bromide and *d*-tubocurarine chloride were compared by assessing their effects on relaxation of skeletal muscle and modification of the electric fit in a series of 50 successive patients undergoing electric convulsion therapy for various psychiatric disorders.

3. (*a*) Davies, D. L., and Lewis, A.: Effects of Decamethonium Iodide (C10) on Respiration and on Induced Convulsions in Man, Lancet **1**:775 (May 7) 1949. (*b*) Hobson, J. A., and Prescott, F.: Comparison of Decamethonium Iodide with *d*-Tubocurarine in Controlling Electrically Induced Convulsions, ibid. **1**:819 (May 14) 1949. (*c*) Grob, D.; Holaday, D. A., and Harvey, A. M.: The Effects of Bis-Trimethylammonium Decane Diiodide and Dibromide on Neuromuscular Function and on Induced Convulsions in Man, New England J. Med. **241**:812 (Nov. 24) 1949.

4. Davies, D. L.: Substitutes for Curare, Lancet **1**:1091 (June 10) 1950.

5. Hobson, J. A., and Prescott F.: (*a*) Use of *d*-Tubocurarine Chloride and Thiopentone in Electro-Convulsion Therapy, Brit. M. J. **1**:445 (April 5) 1947; (*b*) footnote 3b.

Case Material.—The ages of the patients ranged from 17 to 71 years. The diagnostic categories (table) included manic-depressive psychosis, schizophrenia, involutional melancholia, intractable facial pain (1 case) and a "neurotic" depression (1 case). Approximately two thirds of these subjects were outpatients.

Before electric convulsion therapy was instituted, each patient was given physical and neurological examinations; a psychiatric history was obtained, and psychological tests, such as the Minnesota Multiphasic Personality Inventory and the Rorschach test, were administered when indicated. In addition, complete blood counts, a urinalysis, serologic tests of the blood and roentgenographic studies of the chest and the entire spine were made. An electrocardiogram was taken on all patients over 40 years of age and on all other patients in whom there was any indication for such a test. Anteroposterior and lateral roentgenograms of the thoracic portion of the spine were taken at the conclusion of each patient's course of treatments.

Most of this group was found to be free of physical disease, but among them were cases of hypertensive vascular disease, cardiovascular disease, postoperative brain tumor, retinal detachment, arteriosclerotic paralysis agitans and post-thrombotic hemiplegia. A total of 644 treatments were given to 50 patients, and each patient's response was tested with both drugs, 374 treatments being given with decamethonium bromide and 270 with *d*-tubocurarine chloride. Treatments were usually given three times a week at the beginning of therapy and less often later, but occasionally they were given twice a day.

Criteria for Drug Dosage.—In the present study, as gradually increasing doses of either drug were administered with successive treatments it was noted that often very little objectively

Age Distribution and Diagnostic Categories

Diagnosis	Age, Years							Total No.
	Under 20	20-29	30-39	40-49	50-59	60-69	Over 70	
Manic-depressive psychosis	1	1	3	2	5	2	2	16
Schizophrenia	2	7	3	3	0	0	0	15
Involutional psychosis	0	0	0	9	6	2	0	17
Other psychiatric disorders	0	0	1	0	1	0	0	2
Total	3	8	7	14	12	4	2	50

measurable difference in the degree of paralysis or modification of the electric fit was observed over a fairly wide dose range. This range was sometimes as much as 0.5 mg. for decamethonium bromide and 3.0 mg. for *d*-tubocurarine chloride. However, as a subject's upper limits of tolerance to either drug is approached, a fairly sharp end point, at which he can take no more drug without respiratory distress, can be more definitely determined. This increment which results in respiratory "decompensation" was in the order of 0.2 mg. for decamethonium bromide and 1.5 mg. for *d*-tubocurarine chloride. A finer limit may be drawn for the latter, but tests for this were not attempted.

It was felt that a more exact comparison of the efficacy and dosage of these two drugs could be made if to the criteria of maximum peripheral relaxation and modification of the electric fit were added the end point of respiratory tolerance short of respiratory distress. A state of "optimal curarization" may be defined as that in which there is complete or nearly complete peripheral relaxation with marked reduction or total abolition of the tonic and clonic elements of the electric fit in the absence of respiratory distress. The "maximal tolerated dose" would be that dose which is just short of producing respiratory distress in an "optimally curarized" patient. Although a few patients develop slightly more or less tolerance to either drug, it is generally found that once a patient is stabilized on a drug at a maximal level of tolerance, this level is relatively constant for subsequent treatments. The degree of correlation between tolerance levels of one drug with those of the other can be determined and the calculation of equipotent dosage made by comparing the "maximal tolerated dose" for that group of patients in whom an "optimal curarization" effect can be obtained with both drugs.

Technic.—The routine procedure was to give 0.25 Gm. of amobarbital sodium (sodium amytal®) intravenously, followed by the "curarizing" agent, but occasionally mixed with it in the case of decamethonium bromide. The amount of amobarbital sodium was generally sufficient

to render the patient calm and euphoric without actually putting him to sleep. Initial doses were in the range of 1.5 to 2.0 mg. of decamethonium bromide and 7.5 to 12.0 mg. of *d*-tubocurarine chloride (given after a preliminary test dose for sensitivity to the latter). The effect of the drug was assessed and the next dose adjusted appropriately. Even though an almost ideal effect (almost complete relaxation and marked reduction or almost total abolition of muscle tonus and clonus with the electric fit) was obtained at a certain level, the dose was increased in small amounts until definite respiratory distress or "decompensation" was produced. The next lower dose could then be determined as the "maximum" dose tolerated without respiratory difficulty. After this was determined for one drug, the same procedure was undertaken with the other drug. In approximately one-half the patients this "maximum" dose was repeated without amobarbital. Occasionally the patient would not be able to tolerate quite as high a dose of either drug without a preliminary injection of amobarbital, but this was not generally the rule.

All the electric convulsion treatments were given with a machine constructed by the California Institute of Technology. This instrument uses alternating current, 110 volts, and the range of current dosage was 400 to 800 milliamperes for 0.4 to 0.8 second. The current was kept relatively constant for each patient's series of treatments. With the initial treatment decamethonium bromide was administered intravenously at a rate of 1.0 mg. per minute. Subsequent injections in most patients were given at the rate of 2.0 mg. per minute. A few patients exhibited transient dyspnea toward the end of the injection or during the first minute afterward when the drug was given at the latter rate and did not experience this difficulty at a slower rate. On the other hand, a few patients could tolerate their "maximum" dose given at a rate of 1.0 mg. per 10 seconds. *D*-tubocurarine chloride was given at a rate of 3.0 mg. per 10 seconds. When the patient was found unduly sensitive to the respiratory effects of *d*-tubocurarine chloride, the drug was given at a slower rate of 3.0 mg. per 30 seconds, but this only slightly increased the tolerated dose. The electric convulsion treatments were given approximately four minutes after the injection of decamethonium bromide and three minutes after the injection of *d*-tubocurarine chloride had been terminated. The maximum degree of weakness with decamethonium bromide varied with the size of the dose administered, but with the "maximal tolerated dose" the height of weakness was reached usually three to five minutes after injection. It was difficult to determine how long the weakness persisted, since this could not be accurately evaluated in the postconvulsive state. It has been reported by Grob and associates [3c] that it lasts approximately 20 minutes after a dose in the range of the "maximal tolerated dose" described here, in contrast to 40 minutes with curare.

RESULTS

Adequacy of "Curarization."—Using the criteria of complete or almost complete peripheral relaxation and marked reduction or abolition of the tonic and clonic elements of the electric fit in the absence of respiratory distress, the results may be classified as follows:

Group	"Curarization"	No. of Patients
1	Adequate with both drugs	33 (66%)
2	Adequate with decamethonium bromide but not with *d*-tubocurarine chloride	10 (20%)
3	Inadequate with both drugs	7 (14%)

Dosage Range.—Using the maximum dose tolerated without respiratory distress in the group with an adequate response to both drugs (group 1), the results may be expressed as follows:

(*a*) Actual Dose

	Decamethonium Bromide (C 10), Mg.	*d*-Tubocurarine Chloride, Mg.
Minimum	1.8	9.0
Maximum	3.5	24.0
Average	2.6	13.6

(*b*) Dose Expressed in Milligrams per Kilogram of Body Weight

	Decamethonium Bromide	*d*-Tubocurarine Chloride
Mimimum	0.035	0.134
Maximum	0.061	0.375
Average	0.043	0.225[6]

When the 10 patients in group 2 are added to the 33 patients in group 1, making a total of 43 patients responding adequately to decamethonium bromide, the maximum dose of the drug achieved is 5.0 mg. (0.067 mg. per kilogram), and the average dose remains 2.6 mg. (0.042 mg. per kilogram). It appears that the dose of decamethonium bromide required for relaxation is just as unpredictable as is that of *d*-tubocurarine chloride.

Correlation Between Tolerance to Decamethonium Bromide and That to d-Tubocurarine Chloride.—Expressed as the ratio $\frac{\text{mg. } d\text{-tubocurarine chloride (D.T.C.)}}{\text{mg. decamethonium bromide (C 10)}}$ when the maximum dose achieved without respiratory distress in the group with an adequate response to both drugs is used (group 1), the values are as follows:

$$\text{Lowest} = \frac{9.0 \text{ mg. D.T.C.}}{2.4 \text{ mg. C 10}} = 3.75$$

$$\text{Highest} = \frac{21.0 \text{ mg. D.T.C.}}{2.2 \text{ mg. C 10}} = 9.55$$

$$\text{Average} = \frac{13.6 \text{ mg. D.T.C.}}{2.6 \text{ mg. C 10}} = 5.23$$

Thus, on the basis of comparison of doses producing a state of "optimal curarization," the size of the effective dose of *d*-tubocurarine chloride averages 5.23 times and varies in individual patients from 3.75 to 9.55 times that of decamethonium bromide.

Range of Tolerance.—The lowest dose of decamethonium bromide producing respiratory distress in this group of patients was 1.6 mg. (0.029 mg. per kilogram of body weight). The highest dose of the drug tolerated without respiratory distress was 5.0 mg. (0.067 mg. per kilogram of body weight). Comparable doses of *d*-tubocurarine chloride were 6.0 mg. (0.082 mg. per kilogram of body weight) and 24.0 mg. (0.343 mg. per kilogram of body weight).

One patient received as much as 3.0 mg. of decamethonium bromide (0.053 mg. per kilogram of body weight) and 16.5 mg. of *d*-tubocurarine chloride (0.289 mg. per kilogram of body weight) without adequate relaxation. Higher doses of either drug could not be tolerated because of "respiratory decompensation."

Correlation with Age.—The adequacy of responses to either drug was not significantly influenced by age. Each of the five youngest and five oldest of the 50

6. This figure is somewhat less than that of 0.3 mg. per kilogram of body weight of *d*-tubocurarine chloride required for adequate relaxation, as determined by Hobson and Prescott,[5a] but agrees almost exactly with the figure of 0.5 mg. per pound (0.227 mg. per kilogram) reported by A. R. McIntyre (Curare: Its History, Nature, and Clinical Use, Chicago, Ill., University of Chicago Press, 1947, p. 157.) as the "anticipated paralyzing dose" of intocostrin.[8]

patients responded optimally with both drugs. There was some indication that patients of advanced years required slightly higher doses of both drugs, but this was not a uniform finding.

Correlation with Sex.—(*a*) Adequacy of "Curarization": Of the 28 females in the series, 26 (93 per cent) obtained an adequate response with decamethonium bromide and 23 (82 per cent), with *d*-tubocurarine chloride. Of the 22 males in the series, 17 (77 per cent) responded adequately with decamethonium bromide and 10 (45 per cent), with *d*-tubocurarine chloride.

(*b*) Dosage: The average dose of decamethonium bromide for the 10 males in the group responding adequately to both drugs (group 1) was 2.88 mg. (0.042 mg. per kilogram of body weight). The comparable dose of *d*-tubocurarine chloride was 15.5 mg. (0.231 mg. per kilogram). The average dose of decamethonium bromide for the 23 females in this group was 2.44 mg. (0.043 mg. per kilogram), and that for *d*-tubocurarine chloride, 12.8 (0.222 mg. per kilogram).

COMPLICATIONS

Although a goal of maximal "curarization" was sought, no complications were encountered in the 374 treatments given with decamethonium bromide or the 270 treatments given with *d*-tubocurarine chloride. In spite of the fact that the initial dosage was considerably less than the maximum dosage achieved, the protective action of these subparalyzing doses was sufficient to prevent compression fractures of the spine, dislocations or any other complications. Roentgenograms of the thoracic portion of the spine were taken at the end of treatment in every case. It should be stressed that a dose sufficient to produce complete "curarization" to the point of maximal relaxation or respiratory discomfort is unnecessarily high to prevent fractures.

As the dose of either drug was raised to the limits of tolerance without respiratory distress, or slightly beyond this level, certain measures were adopted to speed the return of respiratory function, but it is doubtful whether any of these were necessary. One to 2 cc. of neostigmine methylsulfate (0.5 to 1.0 mg.) was given intravenously immediately after treatment with a high dose of curare. After treatments with maximum doses of either drug it was occasionally felt wise to administer Carbogen (95 per cent oxygen and 5 per cent carbon dioxide) through a mask and to apply artificial respiration by compressing the thorax a few times. However, the apnea was never alarming, and these measures were merely prophylactic. Insufflation of oxygen, provision of an airway or tracheal intubation was never necessary, and respiratory function was always promptly restored. The "curarizing" effects of decamethonium bromide uniformly passed off more quickly than those of *d*-tubocurarine chloride.

Dysphagia was often encountered at maximum levels of either drug but was never a major problem. Two patients of this series reacted to *d*-tubocurarine chloride with bronchospasm, but this did not occur with decamethonium bromide.

In patients undergoing combined insulin coma–electric convulsion treatments it is occasionally advisable to soften the electric fit because of skeletal lesions or as prophylaxis against possible fracture. *d*-Tubocurarine chloride has been found satisfactory for this purpose; but, because its effects last longer than those of

decamethonium bromide, the latter is preferable, as the chances of respiratory complications are less. We have given 47 such treatments to 10 patients receiving insulin coma therapy and no difficulty has been encountered.

In two patients mild thrombophlebitis developed (in one on two occasions) at the site of injection of decamethonium bromide in the concentration of 2.0 mg. per cubic centimeter. This subsided promptly and did not recur when the drug was given in a concentration of 1 mg. per cubic centimeter. Both these patients gave a history of previous episodes of thrombophlebitis with minor trauma.

SUMMARY

The "curarizing" effects of *d*-tubocurarine chloride and decamethonium bromide (C 10; decamethylene-1, 10-bistrimethylammonium dibromide) were compared in a group of 50 patients undergoing electric convulsion therapy for various psychiatric disorders.

The "curarization" effects of the two drugs were essentially similar in 66 per cent of the patients. In 20 per cent adequate relaxation could be produced with decamethonium bromide, whereas respiratory distress without optimal "curarization" was produced with *d*-tubocurarine chloride. In 14 per cent optimal relaxation without respiratory distress could not be obtained with either drug. In no case did *d*-tubocurarine chloride produce optimal "curarization" without the same effect being achieved with decamethonium bromide.

There was no significant correlation between tolerance to one drug and that to the other or between adequacy of response or degree of tolerance to either drug and the age and weight of the patient.

No complications, such as compression fractures or dislocations, were encountered in any patient even when the dose of the drug was insufficient to produce complete relaxation.

Decamethonium bromide is an improvement over *d*-tubocurarine chloride in modifying electric convulsion therapy in that histamine-like reactions are absent, the duration of paralysis is shorter and respiratory distress with intensely "relaxing" doses is less frequent.

CLINICAL AND PHYSIOLOGICAL STUDIES IN A CASE OF MYOKYMIA

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KNY [1] IN 1888, reported a clinical case of a condition which he termed "myoclonus fibrillaris multiplex." The patient was a man aged 50 whose disease was characterized by the gradual onset of cramps and fasciculations. Both conditions occurred in the gastrocnemius muscles, and fasciculations alone were present in the peroneus, rectus abdominis, deltoid, biceps and interosseus muscles. In 1895 Schultze [1] recorded the following case of a disease which he named "myokymia." A man aged 21 was seized with painful cramps in his lower limbs, which, when moved actively or passively, went into spasm. On other occasions brief painful contractions occurred, with tonic plantar flexion of the toes and extension of the great toe. The muscles of the calves and thigh and selected muscle groups of the chest and arms exhibited a constant, sinuous, local fasciculating movement. The feet and legs were bathed in perspiration. Of these two cases, Wilson [2] said, "Whatever these diverse cases may have been, fasciculation is neither the sole nor the outstanding feature of such patently toxic conditions." He surmised the first case to be one of the early phase of an atypical amyotrophic lateral sclerosis. He hesitated to venture a guess in the second case. He failed to recognize "myokymia" as a separate symptom, different from fasciculation.

REPORT OF A CASE

Clinical Description.—The case presented here bore a great resemblance to the two cases described above. The patient, a white man aged 47, was in fair health until 1942, when he first noted the gradual onset of cramping in his calves after arduous exercise. This later occurred in the thighs and in the arms, and after much less exertion. The patient also complained of excessive perspiration, especially of the feet. He complained that his extremities frequently became cold and cyanotic. The condition became worse over the years, and in the past two years the patient had noticed that he was tenser and more anxious. He stated that the cramps and the bulging of the muscles (figs. 1 and 2) in his legs frequently awakened him at night. In 1946, because of the severity of the cramping in his legs, he sought medical advice and, because of the presence of rather severe varicosities in both legs, underwent ligation and injection of the

1. Cited by Wilson, S. A. K.: Neurology, Baltimore, William & Wilkins Company, 1940, vol. 2, p. 1654.

2. Wilson, S. A. K.: Modern Problems in Neurology, New York, William Wood & Company, 1929.

saphenous veins. He stated the belief that the operation improved his condition for about six months. However, the symptoms reappeared and for the past two years had been worse than before.

Physical examination revealed an essentially normal condition except for the muscular phenomena described. Neurological examination revealed that the left leg had about 80 per cent normal strength and the right leg about 60 per cent. There was no atrophy. Stimulation of the muscles, both direct and indirect, with galvanic and faradic current, gave normal responses. The

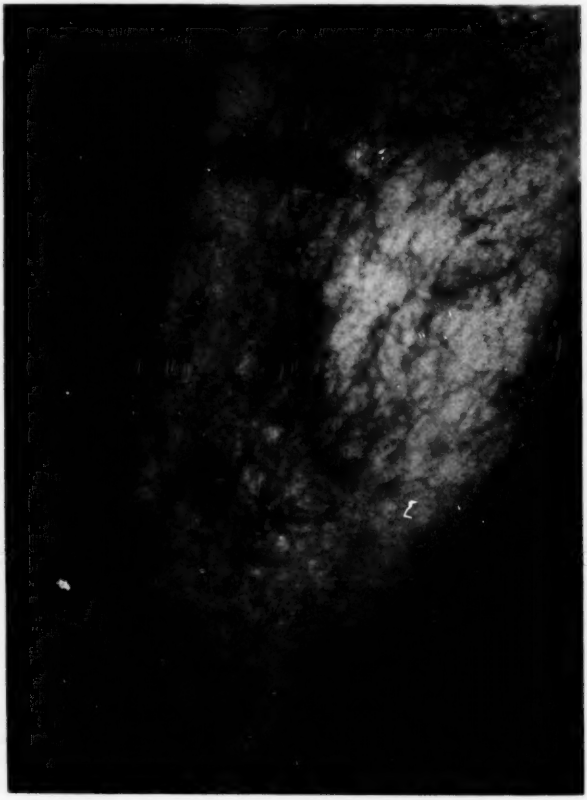

Fig. 1.—Bulging and cramping in the right gastrocnemius muscle (lateral surface).

patient's condition was further characterized by a coarse tremor of the hands and feet. Undulations of the muscles of a rhythmical nature were present; they were most conspicuous in the right gastrocnemius muscle, occurred to a less extent in the left gastrocnemius muscle and were least pronounced in the flexor carpi ulnaris and platysma on the right side and the biceps muscle bilaterally. There was an increase in the myotatic excitability of all muscles, being especially noticeable in those of the thorax. The cranial nerves were unaffected. The reflexes were physiological throughout. Pathological reflexes were not elicited. Sensation was normal for all modalities. Extensive laboratory tests and roentgenographic studies revealed no abnormalities.

Physiological Experiments.—Electromyographic tracings were recorded on a Grass electroencephalographic apparatus converted to electromyographic use. The patient's resting electromyogram was recorded with the use of a coaxial needle electrode. The electrode, patterned after that used by Adrian and Bronk,[3] was inserted in the right gastrocnemius muscle. The tracing revealed a rhythmical undulation, varying in rate from 7 to 8 per second (fig. 3). This was within the limits of normal rates of muscle contraction, according to Hoefer and Putnam.[4]

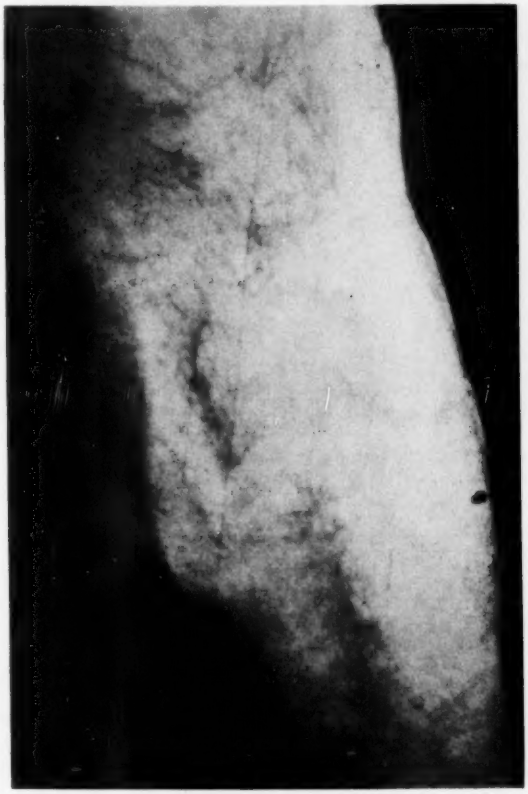

Fig. 2.—Bulging and cramping in the right gastrocnemius muscle (medial surface).

but the contractions differed in not being voluntary. The persistence of this wavelike motion during sleep was also noted (fig. 3*C*). Discharges in the right flexor carpi ulnaris muscle and the right biceps muscle showed the same rate. The rate of discharge placed the site of origin in

3. Adrian, E. D., and Bronk, D. W.: The Discharge of Impulses in Motor Nerve Fibers: The Frequency of Discharge in Reflex and Voluntary Contractions, J. Physiol. **67**:119-151 (March) 1929.

4. Hoefer, P. F. A., and Putnam, T. J.: Action Potentials of Muscles in Normal Subjects, Arch. Neurol. & Psychiat. **42**:201-218 (Aug.) 1939.

the anterior horn cells of the spinal cord. According to the theory of cellular discharge described by one of us [5] (H. H. de J.), this rate fell within that of ankle clonus and could be explained as the effect of rhythmical discharges of the anterior horn cells under the influence of stimulation (fig. 4). Tremor is explained in a similar way. For example, the frequency of activity in the corpus striatum is 5 to 6 per second, and that in the cerebral cortex is 9 per second or higher.

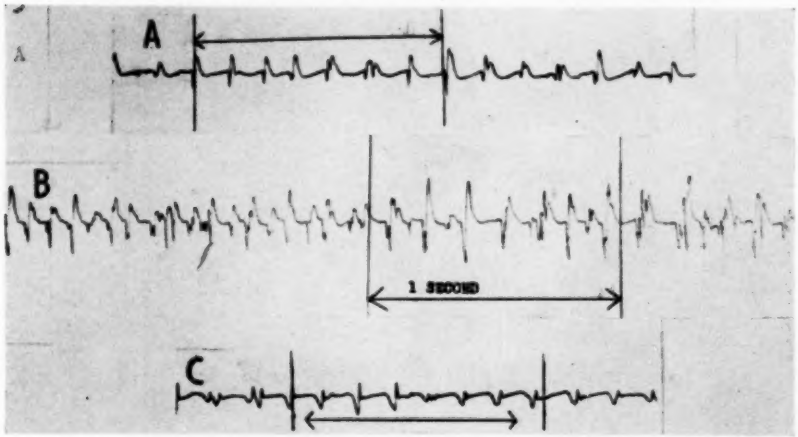

Fig. 3.—*A* and *B*, electromyographic tracings from the right gastrocnemius muscle, with coaxial needle electrode; *C*, tracing taken similarly during sleep.

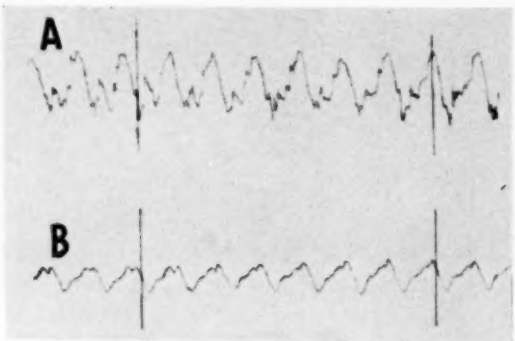

Fig. 4.—Electromyographic tracing during sustained ankle clonus in two cases, with a rate of 7 to 8 per second.

5. de Jong, H. H.: Verdere bevestiging en toepassing van een cellulaire tremor-theorie (Further Confirmation of a Cellular Tremor Theory), Nederl. tijdschr. v. geneesk. **77**:2254-2257 (May) 1933; Phénomène rhythmiques du système nerveux normal et malade, Rev. neurol. **1**:367-377 (March) 1928; Physiological and Psychological Tests in Tremors and Related Phenomena, Nederl. tijdschr. v. geneesk. **1**:472-474 (Jan. 28) 1928.

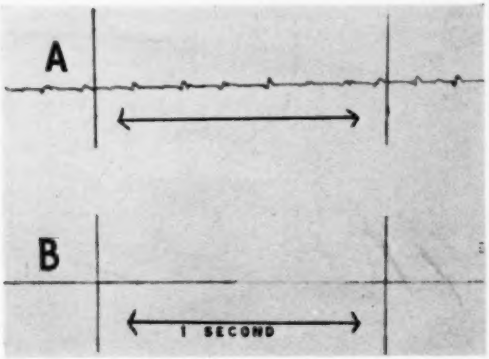

Fig. 5.—Electromyograms from the right gastrocnemius muscle (*A*) before block and (*B*) after procaine block of the tibial nerves.

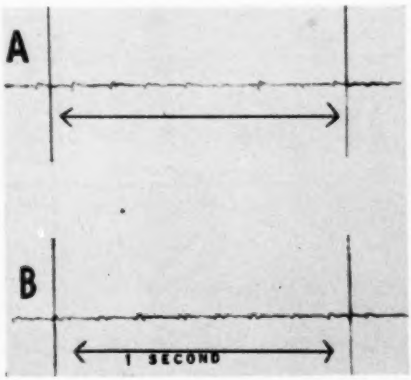

Fig. 6.—Electromyographic tracings from the right gastrocnemius muscle, taken with the coaxial needle electrode (*A*) before and (*B*) after injection of 1.5 mg. of methylsulfate sulfate and 1 mg. of atropine sulfate.

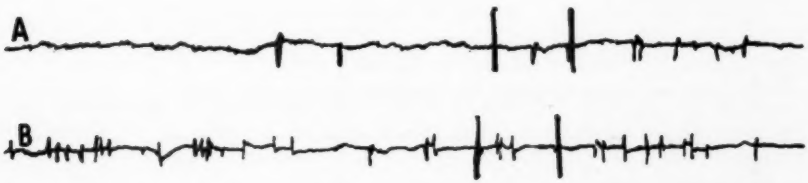

Fig. 7.—Fasciculations in a case of progressive muscular dystrophy (*A*) before and (*B*) after injection of neostigmine methylsulfate, recorded with a needle electrode inserted in an arm muscle. The distance between the heavy vertical lines is ½ second. A definite increase in the amount of fasciculations is evident.

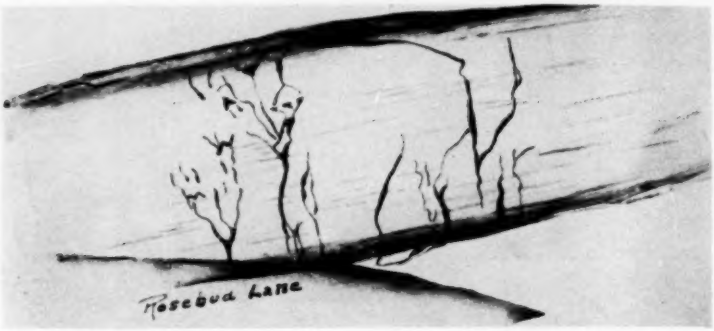

Fig. 8.—Biopsy specimen from the bulging part of the gastrocnemius muscle, showing normal end plates.

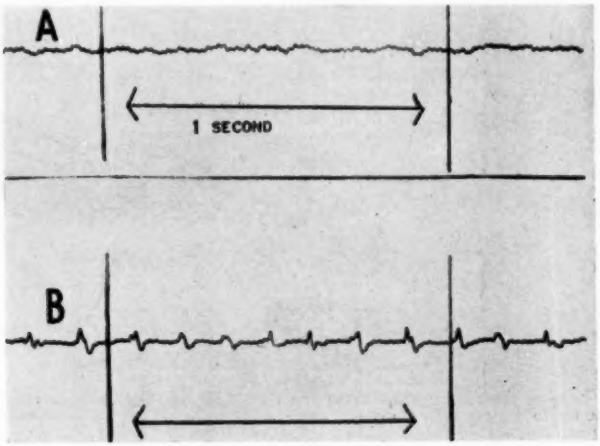

Fig. 9.—Electromyographic tracing from the right biceps muscle (*A*) at rest and (*B*) after 15 quick contractions.

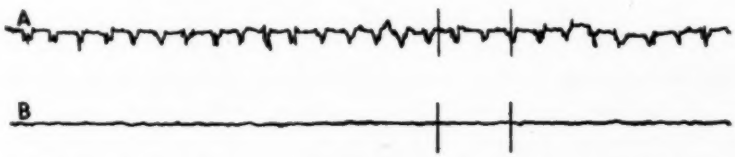

Fig. 10.—Needle recording in a case of paralysis agitans (*A*) before sleep, showing tremor and a mechanogram. In *B*, taken during sleep, the tremor is absent.

Spinal anesthesia caused the cramping and the undulations to disappear completely. Nerve block of the posterior tibial nerve with a 2 per cent procaine solution also abolished the undulations in the gastrocnemius muscle (fig. 5). The completeness of the nerve block was adequately demonstrated by lack of plantar flexion on electrical stimulation of the posterior tibial nerve in the popliteal area. Biopsy of the gastrocnemius muscle at the location of the bulging portion showed that the motor end plates were normal (fig. 8). Furthermore, the response of the undulations in the gastrocnemius and other muscles to neostigmine, quinine, curare, voluntary movements, commands and other stimuli were investigated. There appeared to be no visible change after the injection of 1.5 mg. of neostigmine methylsulfate (fig. 6). This is in contrast to the result in cases of progressive muscular dystrophy with fasciculations (fig. 7).

Differentiating Features of Fasciculation, Tremor, Myoclonus and Myokymia

Feature	Fasciculation	Tremor	Myoclonus	Myokymia
Muscular movements	Arrhythmical twitching in part of muscle	Rhythmical movement of muscle groups	Arrhythmical twitching in part of muscle	Rhythmical undulations in bulging part of muscle
Rate	Irregular	Constant	Irregular incidence	Constant
During sleep	Present	Absent (fig. 10)	Absent	Present
After administration of scopolamine hydrobromide	Present	Absent	Present	Present
After administration of bulbocapnine phosphate	Present	Possibly absent	.....	.....
After administration of neostigmine methylsulfate	Increased	Absence of change	Absence of change	Absence of change
After nerve block	Present	Absent	.....	Absent
After spinal anesthesia	.....	.....	.....	Absent
Effect of impulses for voluntary movement	Activation	.....	Activation	Activation
Effect of mechanical and electrical stimulation of muscle	Activation	.....	Absence of activation	Absence of activation
Reaction to different stimuli, such as pinprick, cold and emotion	Absence of change	Activation	Activation	Absence of change
Muscle atrophy	Usually occurring in atrophic muscles	.....	.....	Absence of muscular atrophy
Reaction of degeneration and increased chronaxia in involved muscle	.....	.....	Absence	Absence
Locomotor effect	.....	.....	Frequent lack	Frequent lack
Ticlike movements	.....	.....	In advanced stages	.....
Tremor	.....	.....	.....	Appearance in intense states
Intense, painful cramp and bulging of muscles involved	.....	.....	.....	Present *
Motor end plates	.....	.....	.....	Normal

* Cramping of the muscles associated with rhythmical oscillations and bulging of these muscles is the outstanding feature of myokymia.

There was no response to quinine, which usually decreases fasciculation. No response to curare was obtained, but it was felt that the small dose used could not have produced much of an effect on the motor end plate. Voluntary movements (fig. 9) first decreased and then increased the amplitude of the undulations, the rate remaining unchanged. Commands and painful, gustatory, visual, auditory, olfactory, thermal and emotional stimuli had no effect on the undulations.

DIFFERENTIAL DIAGNOSIS

The differentiation of myokymia and fasciculation is the most important one, since these two conditions are most frequently confused. The main characteristics of myokymia are (*a*) constant rhythmical rate of discharge, (*b*) absence of increase in frequency or rate on administration of neostigmine methylsulfate.

(*c*) absence of elimination of activity on administration of quinine, (*d*) elimination of activity with peripheral nerve block and spinal anesthesia, (*e*) presence of cramping of muscles and (*f*) normalcy of the motor end plates.

According to previous studies by one of us (H. H. de J.),[6] myokymia can be differentiated from fasciculation, tremor and myoclonus by means of the features indicated in the accompanying table.

SUMMARY

A case of myokymia is presented, with studies which indicated that the condition differs from fasciculation, tremor and myoclonus and should be considered a separate entity, with probable etiological focus in the anterior horn cells of the spinal cord. Further study is indicated to prove or disprove that myokymia is a separate disease entity.

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We wish to acknowledge the assistance of Mr. John C. Murray and Mr. George L. Morin, electroencephalography technicians, in this study.

6. De Jong, H. H., and Simons, D. J.: A Comparative Study of Fibrillation and Tremor, J.A.M.A. **118**:702-705 (Feb. 28) 1942. De Jong, H. H., and Jacobs, L.: A Contribution to the Differential Diagnosis of Myoclonus, J. Nerv. & Ment. Dis. **99**:290-297 (March) 1944.

RETROBULBAR NEURITIS ASSOCIATED WITH HYPERTHYROIDISM

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IN RECENT years, the intensive study of thyroid function by a number of newly developed technics and drugs brought about a gradual reassessment of the classic concept of Graves's disease. While the common hypermetabolic and/or exophthalmic forms of Graves's disease present little diagnostic difficulty, these new methods have made it possible to evaluate peculiar cases in which the symptoms were primarily cardiotoxic or myopathic, or even simulated hyperparathyroidism.[1] We wish to present two cases in which a neuropathic syndrome was outstanding. It may be of interest to note in passing that these two cases were studied in different institutions at different times by different workers, and only a chance hallway conversation served to bring them together. It was not until the case reports were actually written and compared that the remarkable similarities became fully appreciated.

REPORT OF CASES

CASE 1.—F. J., a schoolgirl, was first seen by one of us (T. H. McG.) at the age of 16 years. In childhood she had had chickenpox, rubella and measles without any unusual complications. She had had tonsillectomy and adenoidectomy performed at the age of 9 years because of "mouth breathing." "Yellow jaundice" developed the same year; this lasted nine weeks and preceded the symptoms of her ocular disturbances by six months. Her catamenia was established at the age of 12 years, the menses recurring every 28 days and lasting from four to five days, with profuse flow. It is significant that her father had a thyroidectomy performed at the age of 15 for the relief of hyperthyroidism; her mother suffered from migraine, and an uncle and aunt had diabetes mellitus.

At the age of 10 years the patient had onset of headaches in the left frontotemporal region, occasionally associated with nausea and vomiting. During the following year she became aware of blurring of vision in the left eye. This gradually became worse until, at the age of 15 years, she sought relief for total loss of vision in the left eye. At that time the patient was a thin, mentally alert, apprehensive, nervous girl, perspiring rather profusely. There was total loss of vision in the left eye, without light perception, although the consensual reflex was preserved

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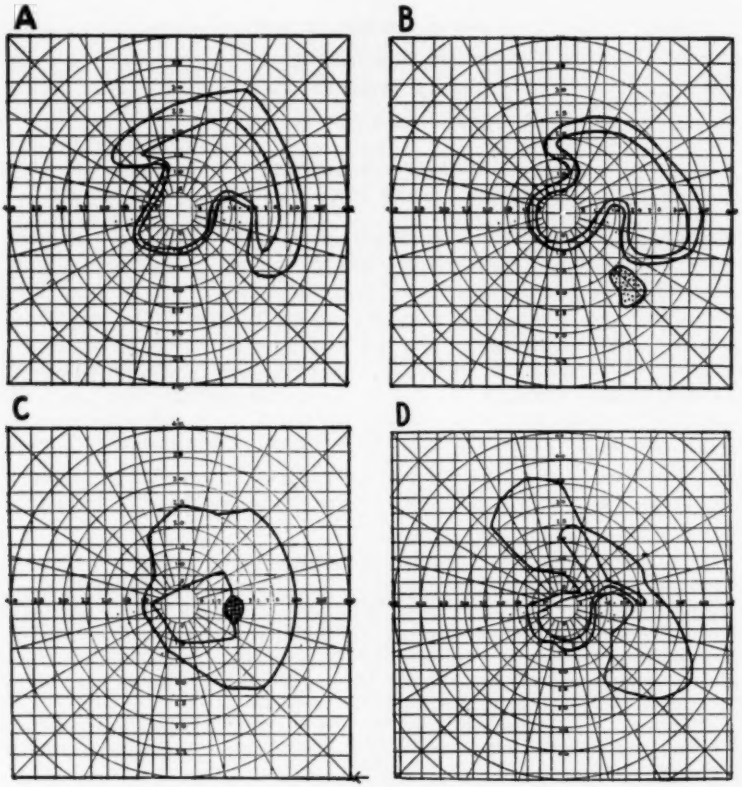
Read by title at the Annual Meeting of the Association for the Study of Internal Secretions, San Francisco, June 24, 1950.

From the Endocrine Division, Department of Medicine, St. Clare's Hospital, and the Department of Medicine, New York Medical College.

1. Stanley, M. M., and Fazekas, J.: Thyrotoxicosis Simulating Hyperparathyroidism, Am. J. Med. **7**:262-268, 1949.

and the pupil responded in accommodation. The fundus on this side showed a papilledema of 3 D. with underlying pallor of the disk. On the right side there were some optic atrophy and nasal constriction of the visual field (figure, *A*). Vision in this eye was 15/20. Readings on the Hertel exophthalmometer were 19 mm. on the right side and 20.5 mm. on the left. On examination the nose and throat were pronounced normal. However, neurological examination revealed hyposmia and mild hyperreflexia on the left side. An electroencephalogram indicated the presence of a diffuse disturbance of cortical activity; a pneumoencephalogram showed a completely normal ventricular system. In each of two examinations of the cerebrospinal fluid, the specimen was



Visual fields of the right eye taken at one year intervals. The outer line indicates the field for 10/1000 white; the inner line, the field for 3/1000 white.

clear, free of white cells and under normal pressure; the values for total protein were 39.5 and 43.0 mg. per 100 ml., respectively, and those for glucose, 205 and 69 mg. per 100 ml. (values for blood sugar, 227 and 82 mg. per 100 ml., respectively); reactions to the Wassermann and Pandy tests were all negative, and the colloidal gold curves were normal. The urine was consistently aglycosuric, nor did it show abnormality in any other respect. The major diagnostic possibilities considered at that time were said to have been retrobulbar neuritis and multiple sclerosis.

About three to four months after the aforementioned examination, the patient became acutely aware of the nervousness and excessive perspiration which were evident at the time of her initial examination. In addition, she also complained of palpitation with a feeling of pressure

over the sternum, dyspnea on exertion, voracious appetite, loss of weight, increasing frequency of headaches and an enlarging neck. However, it was not until one year after the onset of these symptoms that she sought medical advice regarding them. At that time, when she was first seen by one of us, the physical examination revealed a normally developed, somewhat small, undernourished girl, who appeared mentally alert. She seemed highly apprehensive, perspired profusely and had prominent, staring eyes. Her weight was 101 pounds (45.8 Kg.), and her height, 58 inches (142 cm.), with the span 61 inches (155 cm.) and the length from pubis to floor 29 inches (71 cm.). There were complete optic nerve atrophy in the left eye and an atrophy of 50 per cent in the right eye. The Stellwag, Joffroy and Möbius signs were all present. The exophthalmos measured 22 mm. in each eye. A mild acneform eruption was apparent about the mouth and nose. There was a slight tremor of the tongue. The lymph nodes of the posterior cervical triangle were enlarged, discrete and nontender. The thyroid gland was diffusely enlarged, smooth in outline and soft in consistency. A loud bruit could be readily heard over the entire gland, being most pronounced over the right lobe. The heart was hypermotile but not enlarged. The pulse rate was 136 per minute and the blood pressure 130/40. Neither thrills nor murmurs could be detected over the cardiac area. There was still mild hyperreflexia on the left side of the body. No pathological reflexes were present. Nothing noteworthy was revealed in the rest of the physical examination. At this time the diagnosis of hyperthyroidism of the Graves type was confirmed by the finding of a basal metabolic rate of + 75 per cent.

The nature of her ocular condition was still not clear, but retrobulbar neuritis with arachnoiditis seemed to be the most likely possibility. The hyperthyroidism was treated with antithyroid compounds and small doses of strong iodine solution U. S. P. (1 minim [0.06 cc.] daily), with the result that the stare diminished markedly, making the eyes less prominent; exophthalmometric readings made on separate occasions (Sept. 30, 1947; Sept. 11, 1948; Sept. 17, 1949), after full control of the thyrotoxic state, were 21 mm. on the left side and 23 mm. on the right side at each determination. Changes in the visual fields are shown in the figure, *A* to *D*.

In the two years since such treatment was instituted, two unsuccessful attempts have been made to discontinue the therapy. In both instances relapses have been associated with an aggravation of the stare but with no changes in the exophthalmos (left eye, 21 mm.; right eye, 23 mm.) or the activity of the now quiescent retrobulbar process. The patient is at present taking maintenance doses (4 mg. daily) of methimazole (tapazole®) (1-methyl-2-mercaptoimidazole) and strong iodine solution U. S. P. (1 minim every other day).

Case 2.—M. H., a single white nurse, aged 35, was first seen by one of us (M. A. G.) in August 1943. She had a history of transient alopecia areata since childhood, which had developed into permanent alopecia totalis at the age of 32. Urticaria had been noted intermittently for a number of years.

In March 1943 the patient became nervous and lost considerable weight (12 pounds [5.4 Kg.] in one month). At that time the basal metabolic rate was reported as + 38 per cent. Bed rest was instituted for two months, during which the basal metabolic rate fell to — 12 per cent. On Aug. 1, 1943, six weeks after her discharge, the rate was + 3 per cent.

When first seen by one of us, on Aug. 18, 1943, the patient complained only of nervousness; there was no palpitation, hyperhidrosis or diarrhea, and she preferred a warm environment. The menstrual cycle was regular. Physical examination showed a height of 62.25 inches (158 cm.) and a weight of 95.25 pounds (43.2 Kg.). The pulse rate was 92 per minute, and the blood pressure, 130/75. There was no tremor and no exophthalmos or other ocular signs. The skin was smooth but not moist. The thyroid gland was slightly and diffusely enlarged, and the right lobe was of somewhat nodular consistency. There were no abnormal neurological findings.

With 100 to 200 mg. of diiodotyrosine daily and sedation with atropine sulfate and phenobarbital, the weight increased 20 pounds (9.1 Kg.) in seven weeks, the pulse rate dropped to normal (between 72 and 76 per minute), the basal metabolic rate fell to — 27 per cent and the thyroid gland became somewhat larger and firmer. Thereafter, the status fluctuated persistently, except that no further significant variation in weight occurred. At one time the basal metabolic rate decreased to — 32 per cent, while on several occasions the pulse rate became

elevated and a slight stare developed. Thiouracil could not be used because of an allergic sensitivity to the drug; however, the symptoms were controlled fairly successfully with variable doses of diiodotyrosine and sedatives.

In January 1946 the patient received a course of roentgen irradiations of the thyroid. The gland receded in size, and no symptoms were noted for a year. In 1947, however, the tachycardia reappeared but was controlled with small doses of diiodotyrosine. The patient remained well until July of that year, when, during a prolonged and strenuous automobile tour, there developed exophthalmos and marked drowsiness, together with lacrimation and failing vision in the left eye. Examination by an ophthalmologist at that time did not show retinal changes or increased intraocular tension, but revealed a small central scotoma in the left eye and a decrease in visual acuity to 20/200 in that eye. A diagnosis of retrobulbar neuritis was considered.

The patient's next visit to us was made five weeks thereafter. Except for slight nervousness, there were no new complaints. Exophthalmos was now prominent, being 21 mm. on the right and 24 mm. on the left. There were paresis of the left superior rectus and weakness of the left inferior rectus muscle; the central scotoma was still present in the left eye. The weight was unchanged (120 pounds [54.4 Kg.]); the pulse rate was 76; the basal metabolic rate was — 20 per cent, and the serum cholesterol was 308 mg. per 100 ml. A few weeks later there appeared headaches in the frontal region and pains shooting to the left temple, and neurological examination revealed slight weakness of the left sixth cranial nerve and of the left inferior rectus muscle. The pupils were regular and equal; the left reacted sluggishly to light, and the consensual reflex, left to right, was also sluggish. There was slight blurring of the margins of the left optic disk; the right optic disk appeared normal. There was slight hypalgesia of the left half of the body and face. On the left side the biceps, triceps and radial reflexes and the knee and ankle jerks were hyperactive and greater than those on the right. The abdominal reflexes on the left were diminished as compared with those on the right and were easily exhaustible. A Hoffmann sign was elicited on the left side. There was no Babinski, Oppenheim or Chaddock sign or ankle clonus. Equilibratory and nonequilibratory coordination was intact. There was no ataxia, past pointing or motor weakness.

Roentgenographic examination of the skull showed the outline of the skull, the skull markings, the density of the cranial bones, the sella turcica and optic foramens to be normal in appearance. There was no evidence of increased intracranial pressure. The pineal gland was not calcified. There was calcification of the retroclinoid ligament. Electroencephalograms showed "no definite abnormality." Lumbar puncture yielded water-clear fluid, under a pressure of 170 mm. of water. Laboratory examination of the fluid revealed 2 white cells per cubic millimeter, a negative Wassermann reaction and a normal colloidal gold curve. The Wassermann reaction of the blood was also negative. In pneumoencephalograms, ventricles of normal size, shape and position were outlined.

At that time the findings pointed to a lesion of the central nervous system involving the left optic nerve, with mild pyramidal tract signs on the left. Headache and amblyopia suggested a neoplasm, but the acuteness of their onset did not support such a diagnosis, nor did encephalographic studies bear it out. More favored was the possibility of an inflammatory process or multiple sclerosis.

Five months after the onset of this episode of failing vision and neurological changes, there appeared severe nervousness, tachycardia and loss of weight. The thyroid underwent slight, but definite, enlargement despite therapy with diiodotyrosine (300 mg. per day), estrogens (1.25 mg. of estrone sulfate per day) and desiccated thyroid (0.06 to 0.12 Gm. per day). The ocular findings remained unaltered.

On Dec. 8, 1947 a subtotal thyroidectomy was performed. Almost immediately the patient noted improvement in her vision, and nine days after operation the acuity in the left eye was 20/50. The exophthalmos remained undiminished. The retrobulbar and periorbital pains had subsided entirely, and the paresis of the left sixth nerve was not demonstrable. Deep reflexes were bilaterally and symmetrically hyperactive. The Hoffmann sign, previously noted, was not elicited, and the sensory changes were no longer present. Shortly after operation treatment with 0.112 Gm. of thyroid U. S. P. and 2.5 mg. of estrone sulfate daily was again instituted. One month after operation vision in the left eye was 20/40; there was still paresis of the left superior rectus and left inferior oblique muscles. Three and one-half months after operation vision in both eyes was 20/20; exophthalmos and muscular pareses had not changed further.

Summary.—In this case a woman had a 4½ year history of unmistakable Graves's disease in which ocular signs were minimal and the condition was well controlled by intermittent courses of treatment with organic compounds of iodine. During a period of quiescence, in which the status was definitely hypothyroid (as judged by the clinical findings, basal metabolic rate and serum cholesterol), neurotoxic symptoms developed. Five months after the onset of these symptoms active metabolic hyperthyroidism reappeared; the ocular signs persisted. A subtotal thyroidectomy was done at once and resulted in almost instantaneous improvement of the amblyopia, together with disappearance of the changes in the reflexes and a decrease in the symptoms of hypermetabolism.

COMMENT

Involvement of the Optic Nerve.—The course of events manifested by these cases, especially case 2, makes it difficult to escape the conclusion that the thyroid was in some way responsible for the optic neuritis, not to speak of the other neurological manifestations for the moment. In certain respects this is not a novel idea. In 1900 Coppez [2] reported five cases, and in 1902 Aalbertsberg [3] reported another case, in which optic neuritis developed in the course of excessive and prolonged thyroid medication. Fuchs [4] in 1903 stated that "retrobulbar neuritis is not infrequently associated with exophthalmos and paralysis of the external ocular muscles." Birch-Hirschfeld and Inouye [5] were able to produce optic nerve atrophy without vascular changes or papilledema by the administration of enormous doses of "thyroidin" (94 to 1,670 Gm. over a period of 10 months) to each of four dogs. Wegelin [6] also mentioned the existence of optic nerve atrophy in conjunction with hyperthyroidism, and Fridenberg [7] in 1922 stated that "optic atrophy, choked disc and optic neuritis have been noted in Graves's disease . . . and [after] therapeutic use [of thyroid] in myxedema and obesity in women." Szily and Poos [8] mentioned the occurrence of transitory blindness, amblyopia and scotoma in cases of Graves's disease. The remarkable feature of the literature dealing with this subject is the uniform reiteration of these observations without the factual support of a single case report or well documented study. The cases of Coppez and of Aalbertsberg are not concerned with intrinsic hyperthyroidism in the first place, and are at best little more than brief clinical notes.

Disturbances in Cranial Nerves Other Than the Optic Nerve.—Neurological disorders other than those involving the second cranial nerve have also been

2. Coppez, H.: Névrite optique par absorption de thyroïdine, J. de méd., Brux. **5**:641-644, 1900.

3. Aalbertsberg, G.: Neuritis optica door het gebruik van Schildklier, Nederl. tijdschr. v. geneesk. **38**:1125-1129, 1902.

4. Fuchs, E.: Lehrbuch der Augenheilkunde, Vienna, Franz Deuticke, 1903, p. 568.

5. Birch-Hirschfeld, A., and Inouye, N.: Experimentelle Untersuchungen über die Pathogenese der Thyreoidinamblyopie, Arch. f. Ophth. **61**:499-523, 1905.

6. Wegelin, C.: Die Schilddrüse, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Springer-Verlag, 1926, vol. 8, p. 400.

7. Fridenberg, P.: Disorders of Metabolism and Internal Secretions in Relation to the Eye, in Endocrinology and Metabolism, New York, D. Appleton & Co., 1922, vol. 2, p. 789.

8. Szily, A., and Poos, F.: Innere Sekretion und Auge, in Hirsch, M.: Handbuch der inneren Sekretion, Leipzig, C. Kabitzsch, 1933, vol. 3, pp. 1703-1746.

observed in patients with hyperthyroidism. Heuer [9] stated that almost all types and combinations of cranial nerve paralysis, even bulbar forms, have been observed in thyrotoxicosis at some time. Disturbances of innervation of the eyelids and extraocular muscles are by far the most frequently observed and were seen in our case 2. Such observations are not surprising in view of the extent of local pathologic change which may exist in exophthalmos. There is, however, some question as to the nature of such changes—whether they are the result of intrinsic muscular lesions or whether they may also represent damage to the nerve supply itself, on either a mechanical or a toxic basis. Dobyns [10] found that single, large doses of thyrotropic factor can produce extensive histological changes of the extraocular (and other) muscles, consisting chiefly of the appearance of fat droplets in the muscle fibers; no nerve lesions have been described in connection with the administration of thyrotrophic extracts. On the other hand, bulbar forms of paralysis [9] point strongly toward a neural, rather than a muscular, factor. The evaluation of oculomotor disturbances clearly requires a great deal of further study.

Symptoms Referable to the Muscles and Peripheral Nerves.—In those forms of hyperthyroidism featured by myopathic disturbances the oculomotor muscles are usually spared. Both exophthalmos and oculomotor paralyses were notably absent in the cases reviewed by McEachern and Ross [11] and in those reported by Thorn and Eder.[12] Certain of the neurological signs in the cases reported here resemble the findings in cases of myopathic hyperthyroidism, whereas others differ considerably. Hyperactive deep reflexes are not uncommon in myopathic hyperthyroidism (unilateral changes have not been described), and absence of abdominal reflexes has been noted in one case in which myasthenia and wasting were not so severe as to vitiate the importance of this finding. The sensory changes seen by us have not been noted in cases of myopathic hyperthyroidism and appear to be neurogenic manifestations. On the other hand, fatigability, fasciculation or muscular atrophy characteristic of the myopathic disease was not seen in our cases.

In the currently reported cases, the retrobulbar neuritis and the sensory and reflex changes were believed by the consulting neurologists to indicate cerebral neoplasm. However, such a possibility was excluded in both instances by the electroencephalographic and pneumoencephalographic findings. When these were found to afford no positive information, it was concluded by each neurologist that the signs and symptoms were most suggestive of multiple sclerosis.

Dissociation of Thyrotoxicosis and Neurological Manifestations.—One of the outstanding features of case 2 is the dissociation of the neurotoxic and the hypermetabolic phase of the disease. In case 1 the optic nerve atrophy was apparently present about five years before any note was made of nervousness or apprehension, but in the absence of positive evidence of euthyroidism during this period, no

9. Heuer, G. J.: The Cerebral Nerve Disturbances: Exophthalmic Goiter, Am. J. M. Sc. **151**:339-351, 1916.

10. Dobyns, B. M.: Exophthalmos and Tissue Changes in the Guinea Pig Following Administration of the Thyroid Stimulating Hormone of the Pituitary Gland, West. J. Surg. **54**:411-427, 1946.

11. McEachern, D., and Ross, W. D.: Chronic Thyrotoxic Myopathy: Report of 3 Cases with Review of Previously Reported Cases, Brain **65**:181-192, 1942.

12. Thorn, G. W., and Eder, H. A.: Studies on Chronic Thyrotoxic Myopathy, Am. J. Med. **1**:583-601, 1946.

definite conclusions can be reached. In case 2, however, the evidence is indisputable. The neurotoxic symptoms appeared during a period of hypometabolism (basal metabolic rate,—20 per cent; serum cholesterol, 308 mg. per 100 ml.). Tachycardia, nervousness and other signs of thyrotoxicosis did not develop until many months later.

Dissociation of the clinical and chemical findings in hyperthyroidism has been noted in various combinations other than those recorded in the present case studies. Zondek [13] recently described several cases of what he chose to call "mixed thyroidism." In some instances signs and symptoms of hyperthyroidism were present in conjunction with an increased cholesterol and/or a subnormal basal metabolic rate. In one case there were seen an elevated cholesterol level and a low basal metabolic rate, together with signs and symptoms of hyperthyroidism which responded to 0.4 Gm. of "thyroidin" per week, thus illustrating the coexistence of presumably hypothyroid and hyperthyroid symptoms, as well as the response of hyperthyroid symptoms to thyroid medication. Thyrotoxic myopathy shows similar features in some respects, for patients with this condition may exhibit myasthenic symptoms months before nervousness, tachycardia or other signs of thyrotoxicosis appear. In fact, enlargement of the thyroid and ocular signs are notably minimal in this disorder.

Origin of Symptoms.—It has been noted above that ocular changes can be produced by the experimental administration of thyrotropic extracts of the pituitary gland. One might reasonably suspect therefore that disturbed function of the pituitary might also explain some of the unusual features observed in our cases. However, a study of the sequence of events in case 2 shows that one cannot attribute the neurotoxic symptoms to pituitary dysfunction. The major point against such a hypothesis is that the neurotoxic symptoms disappeared promptly on thyroidectomy, whereas those which might have been of hyperpituitary origin (exophthalmos, ophthalmoplegia, etc.) remained unchanged. Moreover, one would expect symptoms due to pituitary dysfunction to become worse, rather than better, after thyroidectomy.

Since the thyroid gland seems definitely implicated, one is faced with two alternatives. First, there is the possibility that the thyroid gland (at least under pathological conditions) is capable of producing more than one biologically active substance and that the secretory activity may therefore show considerable dissociation and independence, e. g., subnormal production of thyroid hormone (metabolic factor), together with pathogenic quantities of abnormal (neurotoxic) substances. The second possibility is that normal thyroid hormone may be metabolized abnormally, with the resultant production of a toxic substance or substances.

Finally, one must consider the theory that the optic nerve atrophy might be the result of a target-organ hypersensitivity to (normal) thyroid hormone. This possibility is contradicted by several observations in case 2. In the first place, the patient had episodes of hyperthyroidism over 4½ years without the development of any visual disturbances. Secondly, the neurotoxic symptoms appeared when the patient was clinically and metabolically in a hypothyroid state, and therefore are not likely to be the consequence of an excess of normal thyroid hormone.

13. Zondek, H.: Mixed Thyroidism, Acta med. orient. **5**:387-390, 1946.

It seems hardly necessary to enlarge on the obvious clinical implications of these cases; but one is inclined to wonder how often occult hyperthyroidism could be demonstrated in puzzling cases of optic nerve atrophy with or without other neurological signs, and, conversely, how often neuropathic symptoms go undetected, even in conventionally well studied patients with thyrotoxicosis.

SUMMARY

Two cases of hyperthyroidism of the Graves type have been described in each of which atrophy of the optic nerve and sensory and motor changes were pronounced features. This condition might well be termed "thyrotoxic neuropathy" or, alternatively, "neurotoxic Graves disease," "Graves's disease with optic atrophy" or "Graves's disease with postbulbar neuritis," thus calling attention to the major differences between it and other forms of thyrotoxicosis.

The appearance of the neurological manifestations was dissociated from the other symptoms of thyrotoxicosis, since they occurred in one patient five years before the hyperthyroid state was treated and in the other patient during a period of hypothyroidism which followed control of the thyroid condition. However, the existence of a relation between the neurological symptoms and the thyroid state seems well proved in case 2, as the symptoms disappeared promptly after thyroidectomy.

The implications and possible pathogenesis of the condition are discussed.

EFFECT OF PREFRONTAL LOBOTOMY ON TEMPERATURE REGULATION IN SCHIZOPHRENIC PATIENTS

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I. COMPARISON OF SCHIZOPHRENIC PATIENTS BEFORE AND AFTER FRONTAL LOBOTOMY

IN RECENT years there has been increasing interest in the physiological aspects of mental disease, with particular attention to the role of the autonomic nervous system. Experience with psychoneurotic illnesses, in which somatic disturbances are associated with emotional tension, has indicated that the autonomic nervous system serves as a connecting link between psychic activity, on the one hand, and visceral function, on the other. This view has been well summarized by Cobb.[1] The observation of physiological disturbances in the psychoses, particularly in schizophrenia, points to such a mechanism. Investigators have sought to place this relationship on a sounder foundation by demonstrating its neurophysiological basis. Since the anterior frontal areas of the cerebral cortex are regarded as the seat of higher psychic activity, it becomes important to investigate their influence on the autonomic nervous system. Until recently, the bulk of such research has depended on animal experiments. To what extent the anterior frontal areas of animals correspond functionally to their anatomic counterparts in humans is open to question. A valuable method of studying the human subject has been introduced with the use of prefrontal lobotomy as a therapeutic procedure. The operation is akin to an ablation type of experiment in that the nature of autonomic representation in the prefrontal cortex may be deduced from changes in autonomic function occurring after lobotomy. Several projects of this type have been undertaken in centers where lobotomy is being used extensively. Rinkel and associates [2] have reported studies of cardiovascular function after lobotomy. They found that the response of the cardiovascular system to autonomic stimulation was exaggerated after operation. Reitman,[3] on the other hand, observed delayed or diminished reactions of the autonomic system to such pharmacologic stimulants as physostigmine, ephedrine

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1. Cobb, S.: Borderlands of Psychiatry, Cambridge, Mass., Harvard University Press, 1943, chap. 9, p. 149.

2. Rinkel, M.; Greenblatt, M.; Coon, G. P., and Solomon, H. C.: Effect of Bilateral Frontal Lobotomy on the Autonomic Nervous System, Am. J. Psychiat. **104**:81-82, 1947; Relation of the Frontal Lobe to the Autonomic Nervous System in Man, Arch. Neurol. & Psychiat. **58**:570-581 (Nov.) 1947.

3. Reitman, F. J.: Autonomic Responses in Pre-Frontal Leucotomy: Preliminary Report, J. Ment. Sc. **91**:318-321, 1945.

and amphetamine after lobotomy. From reports such as these it would appear that autonomic function is altered after lobotomy, in some instances becoming more labile and in others more rigid. It is possible that the nature of the postoperative change may be dependent on the preoperative status of the autonomic nervous system.

With this in mind, we sought in the present investigation to establish the preoperative level of autonomic function in a series of schizophrenic patients by comparing them with normal subjects. It was felt that this would provide a meaningful background for the interpretation of any changes in autonomic activity observed after lobotomy.

One aspect, only, of autonomic function was chosen for study, namely, the regulation of body temperature. Thermoregulation was chosen because it belongs to the sphere of homeostasis, an area of physiology in which the schizophrenic patient has been found particularly deficient.

Emphasis was placed on only two aspects of temperature regulation, namely, the diurnal temperature cycle and the temperature response to prolonged thermal stimuli.

In a previous publication [4a] we have described the preoperative status of temperature regulation in our series of 40 schizophrenic patients. In comparison with the normal controls, the patients exhibited rigidity and irregularity in their regulation of body temperature. Both these abnormalities were manifested in the diurnal temperature cycle, in which the daily temperature rhythm either was reduced or varied greatly from day to day in the timing of maximum and minimum temperatures. Further evidence of rigidity was observed in the response to cold, in that the patients as a group failed to show a continued decline in rectal temperature which occurred in normal subjects after removal from a cold water bath. No difference was found between the schizophrenic and the normal group in the response to heat. The use of the water bath as a form of heat stimulation may, however, distort the true picture, for it is known that the usual forms of heat loss which suffice in air are inadequate in an aqueous medium.

In this communication a comparison will be made of the preoperative and the postoperative pattern of temperature regulation, as revealed by the study of the diurnal cycle and the response to the hot and cold water baths.

CLINICAL SUMMARY

The group comprised 40 schizophrenic patients—38 males and 2 females. The median age was 32 years. The duration of illness at the time of operation varied from one to eight years, with 80 per cent of the patients falling into the two to five year range. Although all subtypes of schizophrenia were represented in the group, the majority of cases (63 per cent) were of the paranoid type.

DIURNAL TEMPERATURE CYCLE

For a period of four days, the rectal temperature was taken at four hour intervals throughout the day and night, giving a total of 24 readings. All readings were made with clinical rectal thermometers calibrated against a standard thermometer. This investigation was carried out for each patient just prior to lobotomy and was repeated six weeks after operation.

The graphic records of the diurnal cycles for three patients are shown in chart 1 (patients Is., De. and Be.). These patients were selected because they are representative of the whole group. In examining these records, one must bear in mind

4. Buck, C. W.; Carscallen, H. B., and Hobbs, G. E.: Temperature Regulation in Schizophrenia: (*a*) I. Comparison of Schizophrenic and Normal Subjects; (*b*) II. Analysis by Duration of Psychosis, Arch. Neurol. & Psychiat. **64**:828-842 (Dec.) 1950.

that the normal subject has a regular diurnal temperature rhythm, characterized by a gradual progression from a minimum temperature, in the early morning, to a maximum temperature, in the late afternoon.[4a]

PATIENT Is. (chart 1 *A*).—The difference between the preoperative and the postoperative records of this patient is striking. Before lobotomy little or no diurnal temperature rhythm was evident, whereas after operation there were fairly regular diurnal fluctuations.

PATIENT De. (chart 1 *B*).—The preoperative record of this patient was characterized by irregularity both in the magnitude of the temperature swing and in the timing of the maximum and minimum temperatures. The postoperative record reveals a much more regular type of cycle.

PATIENT Be. (chart 1 *B*).—In the preoperative cycle of this patient there were broad temperature swings based on abrupt changes in temperature, rather than on the smooth progression from maximum to minimum points which characterized normal subjects. The postoperative temperature cycle resembled the normal pattern.

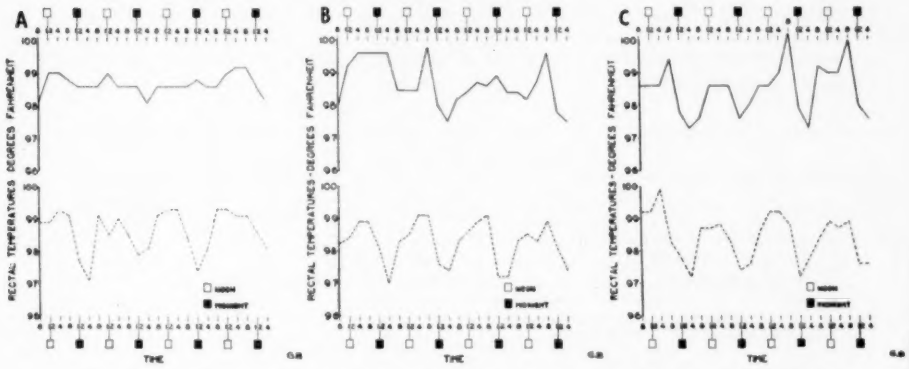

Chart 1.—Rectal temperatures before (solid line) and after (broken line) for three patients: (*A*) Is., (*B*) De. and (*C*) Be.

The abnormalities illustrated by the preoperative records of these three patients were found commonly in the schizophrenic group as a whole, with a tendency for the temperature cycles to revert to a more normal configuration after lobotomy.

In our previous publication [4a] we outlined the measurements which were made in order to compare statistically the diurnal temperature cycles of the patients with those of the normal subjects. A similar technic was employed for comparing the preoperative and postoperative data. This involved the following calculations: (1) the mean temperature over the four day period; (2) the temperature range for each day, from which a mean value was obtained; (3) the day-night differential, i. e., the mean of the day temperatures minus the mean of the night temperatures over the entire four day period.

From the individual means, group means were calculated and compared.[5] The comparisons are shown in table 1. (The group means were not weighted, since all the individual means were obtained from the same number of temperature readings.)

5. Differences between means were tested for significance, using the formula based on the standard error of the mean. The p value represents the percentage probability of obtaining purely by chance a difference as great as the one observed. A p value of less than 0.05 was accepted as significant.

Preoperatively the measurements of the schizophrenic group for mean rectal temperature, for mean daily temperature range and for day-night differential were significantly smaller than those of the normal group. Postoperatively the mean rectal temperature and the mean daily range were unchanged from the preoperative level. There was, however, a significant increase in the size of the day-night differential. In spite of this increase, the postoperative value still differed significantly from normal. The question arises as to how the day-night differential may change without a concomitant change in the mean daily range of temperature. Two situations in which this would occur may be pointed out, using the patients' graphic records for illustration:

1. In the case of patient De. (chart 1 *B*) there were adequate preoperative swings of temperature on all but one of the four days, but obviously with considerable difference from day to day in the timing of these fluctuations. As a result, there was little over-all difference between day and night temperatures. After operation the daily ranges were of no greater magnitude but their size and timing were consistent from one day to another, giving a greater difference between the day and night temperature means (e. g., the preoperative and postoperative measurements, respectively, were 1.7 and 1.7 F. for the mean daily range and +0.07 and +1.1 F. for the day-night differential).

TABLE 1.—*Measurements* of the Diurnal Temperature Cycle in Forty Schizophrenic Patients Before and After Lobotomy*

	Preoperative	Postoperative	Significance of Difference
Daily range of temperature.....	1.5 (± 0.09) †	1.5 (± 0.09) †	.....
Day-night differential.....	+ 0.5 (± 0.06) †	+ 0.7 (± 0.05) †	$p < 0.05$
Rectal temperature.....	98.5 (± 0.06) †	98.5 (± 0.05) †	.....

* Group mean values, expressed in degrees (F.).
† Significant difference from normal.

2. In the case of patient Be. (chart 1 *C*), the daily ranges actually were larger before than after operation, but, as noted, the configuration of the two temperature curves was quite different. The preoperative curve was spiked, whereas the postoperative curve was more sloping. Thus, most of the preoperative temperature readings were close together, with a few extreme values interspersed. This would result in a lower value for the day-night differential. (Preoperative and postoperative measurements, respectively, were 2.1 and 1.8 F. for the mean daily range and +1.0 and +1.0 F. for the day-night differential. Thus, with a reduction in mean daily range, the day-night differential remained unchanged.)

In the case of patient Is. (chart 1 *A*), in which the preoperative cycle was flat and the postoperative cycle swinging, one would expect both measurements to be increased postoperatively. (Preoperative and postoperative measurements, respectively, were 0.8 and 1.7 F. for the mean daily range and + 0.4 and + 0.8 F. for the day-night differentials.)

It appears, therefore, that the day-night differential may be regarded as a finer indication of the normality of the temperature cycle than the mean daily range.

RESPONSE OF BODY TEMPERATURE TO HEAT AND COLD

Thirty-four members of the schizophrenic group were studied before and after lobotomy in hot and cold water baths, to observe the effect of changing environmental heat on the rectal temperature.[6] The constant flow bath with thermostatically controlled water temperature was selected as a convenient medium. At the beginning the temperature of the water was in the

6. Six members of the group, because of physical condition or behavior, were unable to be tested in the baths.

neutral zone (96.0 to 96.8 F.), rising for the hot bath to a temperature of 102.0 F. and falling for the cold bath to a temperature between 60.0 and 70.0 F. Each bath was of two hours' duration. The temperature extremes were maintained for approximately the last half-hour of the bath period.

The patient's rectal temperature was taken at 15 minute intervals during the bath and during the rest period of one hour which followed. A more detailed description of the bath and of the technic for recording the rectal temperature has been given in a previous publication.[4a]

No significant difference was found between the patients' preoperative and postoperative responses to the hot bath. In both reactions the patients differed little from the normal.

This was not true in the case of the cold bath. Very definite differences between the preoperative and the postoperative patterns of response were observed. Such differences are well illustrated by the individual graphic records shown in chart 2.

PATIENT Bl.—This patient's record is most typical of the group as a whole. Preoperatively, his response was characterized by an elevation of rectal temperature following the bath. Postoperatively, the rectal temperature continued its downward course during the period after the bath.

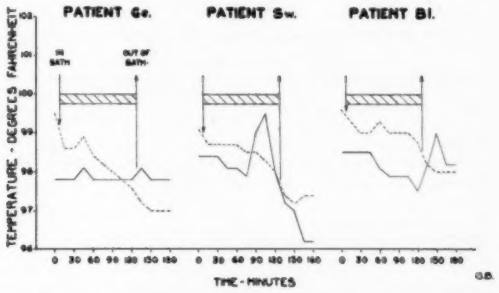

Chart 2.—Individual rectal temperatures in and after the cold bath before (solid line) and after (broken) prefrontal lobotomy.

PATIENT Ge.—The preoperative record of this patient shows a striking resistance to the cold stimulation. The rectal temperature was maintained at almost a steady level throughout the bath and during the subsequent hour. The postoperative record shows a much more flexible response, with a definite fall in rectal temperature during and after the bath.

PATIENT Sw.—In the preoperative reaction of this patient a striking compensatory rise in rectal temperature occurred during the course of the bath. This was not found postoperatively.

The postlobotomy change in the response to the cold bath brought each of these patients closer to the normal pattern, for it has been shown that the normal subject suffers a drop in rectal temperature during the course of a cold bath, which continues for almost a full hour after removal from the bath. The explanation of this phenomenon has been discussed in a previous paper.[4a]

To evaluate the postlobotomy status of the whole group, a statistical analysis of the response to the cold bath was made. This was based on the following measurements:

1. The total change in temperature during the bath—the difference between the rectal temperature reading prior to the bath and the last reading taken in the bath.

2. The total change in temperature after the bath—the difference between the last reading in the bath and the final temperature reading at the end of the hour after the bath.

3. The 15 minute change in temperature after the bath—the difference between the last reading in the bath and the first reading taken after removal.

A comparison of the group mean values is shown in table 2.

In the temperature change after the bath, one finds for the group as a whole a significant difference after operation. Both the total and the 15 minute fall in temperature were significantly increased above their preoperative level. In the latter measurement there was no significant difference between the postoperative value and the normal.

COMMENT

In this group of schizophrenic patients, definite changes in the pattern of temperature regulation were evident after prefrontal lobotomy. Such changes were observed both in the diurnal temperature cycle and in the response to the cold bath. There was a lessening of irregularity in the diurnal cycle, as indicated by the

TABLE 2.—*Measurements* of Temperature Response to Cold Bath in Thirty-Four Schizophrenic Patients Before and After Lobotomy*

	Preoperative	Postoperative	Significance of Difference
Total change in temperature during bath....	−0.5 (± 0.13) †	−0.4 (± 0.12) †	.....
Total change in temperature after bath.....	−0.2 (± 0.16) ‡	−0.6 (± 0.09) ‡	$p < 0.05$
15 minute change in temperature after bath..	−0.02 (± 0.09) ‡	−0.3 (± 0.06) †	$p < 0.05$

* Group mean values, expressed in degrees (F.).
† No significant difference from normal.
‡ Significant difference from normal.

significant increase in the day-night differential. Greater flexibility of temperature control was apparent in the response to the cold bath, with a more marked drop in rectal temperature after removal from the bath. As a result of these changes, the postoperative character of temperature regulation was closer to that of normal subjects.

The occurrence of abnormalities of temperature regulation in schizophrenic patients before lobotomy with a modification of such abnormalities after prefrontal lobotomy indicates that the prefrontal cortex may be implicated in their production. We may postulate that in the schizophrenic psychosis the prefrontal cortex exerts a disturbing influence on the lower autonomic centers concerned with homeostatic function, particularly the hypothalamus. There is adequate evidence for the existence of neural pathways through which the prefrontal impulses could be mediated to the hypothalamic nuclei. The studies of Grinker and Serota [7] and of Murphy and Gellhorn [8] have demonstrated these connections very clearly. It is suggested that the operative interruption of prefrontal connections reduces the disturbing cortical influence, permitting a more normal type of function.

7. Grinker, R. R., and Serota, H. M.: Studies on Cortico-Hypothalamic Relations in Cat and Man, J. Neurophysiol. **1**:573-589, 1938.

8. Murphy, J. P., and Gellhorn, E.: Further Investigations on Diencephalic-Cortical Relations and Their Significance for the Problem of Emotion, J. Neurophysiol. **8**:431-447, 1945.

An alternative interpretation of these findings would be to attribute the postoperative change in temperature regulation to a generalized improvement in the physical and mental status of the patient, rather than to a specific interruption of cortical control over lower autonomic centers. A comparative analysis of the improved and unimproved patients failed, however, to support this explanation. The clinically unimproved group showed postoperative changes in thermoregulation which differed little from those of the improved group of patients.

II. ANALYSIS ACCORDING TO DURATION OF PSYCHOSIS

In a previous publication,[4b] emphasis was placed on the relation which appears to exist between the status of thermoregulation in schizophrenia and the duration of the psychosis. In the present report, changes in temperature regulation occurring after prefrontal lobotomy have been described for a group of patients with psychoses

TABLE 3.—*Measurements* of the Diurnal Temperature Cycle in Group A Before and After Lobotomy*

	Preoperative	Postoperative	Significance of Difference
Daily temperature range	1.3 (± 0.09) †	1.4 (± 0.08)	.....
Day-night differential	+ 0.4 (± 0.07) †	+ 0.6 (± 0.05) †	$p < 0.05$

* Group mean values, expressed in degrees (F.).
† Significant difference from normal.

TABLE 4.—*Measurements* of the Diurnal Temperature Cycle in Group B Before and After Lobotomy*

	Preoperative	Postoperative	Significance of Difference
Daily temperature range	1.9 (± 0.15) †	1.6 (± 0.13)	.....
Day-night differential	+ 0.8 (± 0.12) ‡	+ 0.7 (± 0.09)	.....

* Group mean values, expressed in degrees (F.).
† No significant difference from normal.
‡ Difference from normal approaching significance ($p = 0.06$).

of varying duration. The question arises as to whether the postoperative change in function is uniform throughout the group or whether it varies according to the patient's length of illness at the time of operation.

To answer this question, the data were further analyzed, the patients being divided arbitrarily into two subgroups according to their clinical histories:

Group A: Patients whose psychosis at the time of operation was of four years' duration or less (24 patients).

Group B: Patients whose psychosis at the time of operation was of more than four years' duration (16 patients).

For each group a separate comparison was made of the preoperative and the postoperative measurements for both the diurnal temperature cycle and the response to the water baths.

THE DIURNAL TEMPERATURE CYCLE

The measurements for the diurnal temperature cycle are shown in table 3 for group A and in table 4 for group B.

Only in group A was there a significant change in the diurnal temperature measurements after lobotomy. This group of patients showed a significant increase in the day-night differential. In spite of this increase, the group still differed from the normal after operation. Group B, which differed little from the normal before lobotomy, showed no significant change in either measurement after operation.

RESPONSE TO HOT AND COLD BATHS

Neither group A nor group B showed any postoperative change in the response to the hot bath.

The measurements for the cold bath are shown for group A in table 5 and for group B in table 6. Group A, which before operation had less fall in temperature after the cold bath than did normal subjects, showed a significant change in these

TABLE 5.—*Measurements* of Temperature Response to Cold Bath in Group A Before and After Lobotomy*

	Preoperative	Postoperative	Significance of Difference
Total change in temperature during bath.....	−0.5 (± 0.18) †	−0.5 (± 0.14)	.....
Total change in temperature after bath.....	−0.1 (± 0.22) ‡	−0.6 (± 0.12) ‡	$p < 0.05$
15 minute change in temperature after bath.....	+0.1 (± 0.13) ‡	−0.3 (± 0.05) †	$p < 0.05$

* Group mean values, expressed in degrees (F.).
† No significant difference from normal.
‡ Significant difference from normal.

TABLE 6.—*Measurement* of Temperature Response to Cold Bath in Group B Before and After Lobotomy*

	Preoperative	Postoperative	Significance of Difference
Total change in temperature during bath.....	−0.4 (± 0.17) †	−0.1 (± 0.21) ‡	.....
Total change in temperature after bath.....	−0.5 (± 0.23) §	−1.0 (± 0.11) †	$p = 0.056$
15 minute change in temperature after bath....	−0.2 (± 0.11) †	−0.4 (± 0.11)	.....

* Group mean values, expressed in degrees (F.).
† No significant difference from normal.
‡ Significant difference from normal.
§ Difference from normal approaching significance ($p = 0.056$).

measurements after lobotomy. There still remained a significant difference from the normals in the total change in temperature after the bath, but not in the 15 minute change in temperature.

Group B, which differed from the normal before operation only in the total change after the bath, showed a significant increase in this measurement after lobotomy, resulting in a mean value identical with that of the normal group.

When the response to the cold bath of the whole lobotomy group was examined, no difference from normal was noted in the change in temperature during the bath, either before or after lobotomy. It is apparent from table 6, however, that after operation group B showed less drop in temperature during the bath. Although the difference between the preoperative and the postoperative measurements was not large enough to be significant, the difference between the postoperative measurement and the normal did attain a significant level.

COMMENT

A more revealing analysis of the postoperative changes in temperature regulation is derived from a separate study of the early and the chronic group of patients, which were shown to differ from each other prior to lobotomy. The patients with earlier psychoses (four years' duration or less) exhibited the postoperative changes in temperature regulation which have been described for the group as a whole. This is not unnatural, since this group of patients constituted 60 per cent of the total. The more chronic group, whose temperature regulation resembled the normal before operation, showed little change after lobotomy. Their temperature response after the cold bath, which differed only slightly from the normal preoperatively, was found to be identical with the normal postoperatively. In other words, the patients with earlier psychoses reverted after lobotomy to a type of temperature regulation which was comparable in many ways to that of the chronic patients before operation.

These observations suggest that with increasing chronicity of the schizophrenic psychosis there is a gradual waning of the disrupting influence of the prefrontal cortex on lower autonomic centers. The same effect is achieved more abruptly by prefrontal lobotomy.

SUMMARY OF PARTS I AND II

In this report, postlobotomy changes in temperature regulation are described for a group of 40 schizophrenic patients. These changes brought the patients closer to the normal through a lessening of irregularity and rigidity in the pattern of temperature regulation. The postoperative change was greater in those subjects who differed most from the normal before operation, namely, in the group with relatively early psychoses.

In the interpretation of these findings, it is suggested that the preoperative abnormalities result from the disturbing influence of the prefrontal cortex on lower autonomic centers. This disturbance would appear to diminish naturally as the psychosis approaches chronicity, and to be removed artificially by lobotomy.

CLINICAL AND PSYCHOLOGICAL INVESTIGATION OF PREFRONTAL LOBOTOMY IN CHRONIC SCHIZOPHRENIA

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THE INVESTIGATIONS to be reported here represent an attempt to give a well rounded picture of the reactions of a group of patients with malignant chronic mental illnesses to psychosurgery. It is hoped that this study, in conjunction with the report of physiological findings in the same group, will serve that purpose. Clarification of the value of this treatment in such a situation is badly needed, not only from the standpoint of specific responses but also in order to estimate what can be expected with the widespread use of this treatment in the chronic psychotic hospital population. The findings reported here certainly do not supply the final answer to such a question. Nevertheless, they may serve as an incentive to more extensive exploration along such lines.

Chronic schizophrenia represents the therapeutist's defeat in mass form. There is no better example in the field of medicine. Each successive new therapeutic development is greeted with enthusiasm as the possible answer to the problem but, in the end, is only a nibbling at the edges as far as the total picture is concerned. This has been the case with insulin and electric shock therapy. The acute external reflections of the disease can now be controlled, but the more intimate and basic features of it are still baffling.

The question now arises whether psychosurgery, one of the more recent therapeutic methods, has prospects of offering any more hope. Articles appearing in the literature are not overly encouraging. Usually the palliative effects are emphasized. Unfortunately, however, results tend to be expressed in terms of whether the patient leaves the hospital or not, without specific mention of the changes observed in the basic psychotic features. Rothschild and Kaye,[1] in one of the more searching investigations of the effects of lobotomy on schizophrenia, concluded that lobotomy fails to produce any noteworthy improvement in the basic psychopathologic disturbances of the disease. Freeman and Watts [2] implied only a limited improvement when they stated, in speaking of the schizophrenic, "Instead of taking patients away from the psychiatrists, it is probable that psychosurgery will increase the number of patients in need of psychiatric care as contrasted with custodial care."

1. Rothschild, D., and Kaye, A.: The Effects of Prefrontal Lobotomy on the Symptomatology of Schizophrenic Patients, Am. J. Psychiat. **105**:752-759, 1949.

2. Watts, J. W., and Freeman, W.: Prefrontal Lobotomy: Indications and Results in Schizophrenia, Am. J. Surg. **75**:227-230, 1948.

The most unfortunate and most criticized feature of this treatment is the more or less severe personality impairment which is an almost inevitable result. This feature was remarked on by Ström-Olsen and Tow [3] in their investigation of the social aspects of prefrontal lobotomy. They stated in part: " . . . it can be shown that the psychiatric recovery is often gained at the expense of great reductions of the efficiency, enjoyment, and acceptability of the person." It would appear that this personality impairment, along with the decrease in affective tone and a certain loss of interpersonal warmth, forms the more philosophical objection to the treatment, "loss of soul."

Justification for the widespread use of this treatment in the chronic psychotic hospital population depends in the end, therefore, on which of these features is predominant. In other words, does the improvement obtained outweigh the personality deficits which result? It would appear to us that only unbroken observation of a group of lobotomized patients, rather than intermittent spot sampling, will give the answer. To a considerable degree we feel that this opportunity has presented itself to us. We shall amplify this statement in the discussion of our clinical material.

The present report on our findings should be regarded as preliminary. The time elapsed is not sufficient to permit an answer to such questions as we have posed. It is anticipated that subsequent investigation will place us in a sounder position to do this. The present report covers, in the main, the more immediate reactions of a chronically ill group, specifically those occurring in the six months following operation.

CLINICAL MATERIAL

The present report covers an investigation completed on a group of 49 lobotomized patients from the psychiatric wards of a veterans' hospital. As stated, this study covers the six months' postoperative period. Although our total surgical series is substantially larger than this, the postoperative time which has elapsed for the remainder of the group is not sufficient to permit inclusion of their data in the present report. Similar investigations are being carried out on each patient, however.

The series of 49 patients includes 44 men and 5 women. All the patients have a schizophrenic illness of long standing with a heavy weighting in the direction of the paranoid type. The studies do not involve differentiation along the lines of sex or diagnosis.

The prearranged status of the group within the hospital was entirely therapeutic in its purpose. At the same time, the advantages presented for study and research are obvious. The majority of these patients have been maintained as separate and distinct from other treatment groups. Only the minority who have become too overtly disturbed have had to be returned to the general psychiatric wards. The lobotomy patients have had a postoperative retraining regimen of their own and have been supervised by a relatively constant staff of nurses and attendants. Early postoperative discharge has been neither planned nor attempted. Even those patients who have been discharged from the hospital have had the benefit of the retraining program for a matter of months rather than weeks. Therefore, we can say that the observation of these patients has taken place in a uniform environment and for a matter of months at a minimum.

Each patient has been subjected to the same operation within the limits of the technical ability of the surgeon. The superior open approach with the same technic of section has been used in each case. No serious postoperative neurological or physical complications have arisen to becloud the issue in any case. Postoperative physical factors are not considered, therefore, to have played any part in the ultimate results.

3. Ström-Olsen, R., and Tow, P. M.: Late Social Results of Prefrontal Leucotomy, Lancet 1:87-90, 1949.

The chronicity of the illnesses is emphasized by the fact that none of the psychoses were less than two years in duration. For each of these patients lobotomy can be looked on as a therapy of "last resort." This means, of course, that the treatment which had been administered in the earlier stages of the illnesses had been considered to be without benefit. Further details relative to length of illness and previous treatment will be discussed later in the paper.

TYPES OF INVESTIGATION

Three preliminary studies are reported on in the present paper. Two of these are concerned exclusively with clinical investigation and observation. The third, on the other hand, involves psychometric testing and a condensation of the results obtained.

These three lines of approach may be described as follows:

1. A comparative study of group trends as reflected by behavioral and symptomatic changes before operation and at various postoperative time levels.

2. An estimation of the value of certain factors as criteria for improvement with lobotomy. Specifically, these factors are age, length of illness and reaction to previous treatment, namely, insulin and electric shock.

3. A comparative study of the changes in intellectual functioning as reflected by the findings with the Wechsler-Bellevue scale prior to operation and at various postoperative time levels.

As already pointed out, these studies are complete only to the end of the six month postoperative period. It is felt that a two year study of the entire group is the minimum that should be attempted. In order that this may be accomplished with a sufficiently large clinical material, an over-all period of four years will be necessary.

I. GROUP TRENDS AS REFLECTED BY BEHAVIOR AND SYMPTOMS

The observer who has been intimately associated with this form of treatment of the schizophrenic patient is inevitably impressed with the marked alteration in the patient's behavior. The literature has emphasized the elimination of disturbed, destructive and implusive behavior which more frequently than not follows the operation. With the chronic and consistently disturbed schizophrenic, this can only be looked on as worth while, even though apathy and lethargy may be accompanying features. The question of how permanent and how genuine an improvement this may prove to be is of considerable importance. That there is a rather profound cerebral dislocation and that in the immediate postoperative period there is bound to be an element of organic overlay cannot be ignored. Jones[4] concluded from his investigations that almost half the patient improvement in his series took place by the end of the third postoperative week and might be attributed to the operation itself. He found little evidence of improvement in behavior between the third and the sixth postoperative month. This observation corresponds, by and large, to the trends that have been apparent in our group. However, a question which requires further clarification is the possible tendency toward relapse or toward reversion to the former type of disturbed behavior. To offer a prognosis without these possibilities clearly in mind can only, in the end, defeat its own purpose and undermine confidence in the treatment.

The same queries can be made in regard to more precise symptoms of the schizophrenic state, such as delusions and hallucinations. Tompkins[5] remarked

4. Jones, R. E.: Personality Changes in Psychotics Following Prefrontal Lobotomy, J. Abnorm. & Social Psychol. **44**:315-328, 1949.

5. Tompkins, J. B.: A Summary of 36 Cases of Lobotomy, Am. J. Psychiat. **105**:443-444, 1948.

that hallucinations are often the apparent cause of failure to make a good adjustment after lobotomy and commented on the varying response to them after operation. Other authors [6] have noted the lessened emotional response to these symptoms and have considered their possible eventual elimination. But, again, the permanency of such effects should be more firmly established.

Our studies of group trends include not only behavior, delusions and hallucinations, but also affect. The establishment of trends as reflected by these four features should cover the major areas of change as a result of the operation. The accompanying graphs show the situation as it applies to each of these factors at the four time periods and illustrate the changes more forcibly than would description alone. In each case certain arbitrary standards had to be chosen, but these were made as simple as possible in order not to confuse the issue. Obviously, the nature

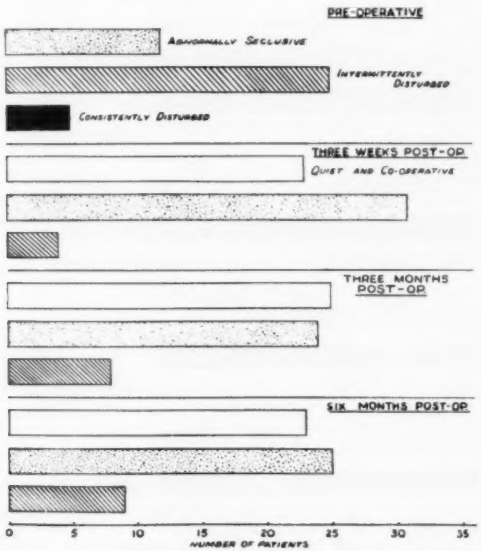

Chart 1.—Behavioral changes before and at stated intervals after prefrontal lobotomy for chronic schizophrenia.

of this particular study does not lend itself to statistical evaluations, and it is emphasized again that the present investigation involves only a demonstration of group trends.

Behavior is an extremely difficult feature to classify, being a diffuse reaction to many stimuli. As will be noted in chart 1, it has been broken down into four simple categories, namely, (1) quiet and cooperative, (2) abnormally seclusive, (3) intermittently disturbed and (4) consistently disturbed. Of course, the behavior of certain patients may fall into more than one of these categories, for example, abnormally seclusive and intermittently disturbed.

6. Freeman, W., and Watts, J. W.: Prefrontal Lobotomy: Convalescent Care and Aids to Rehabilitation, Am. J. Psychiat. **99**:798-806, 1943.

The group prior to operation is essentially a disturbed one, none of the 49 being described as quiet and cooperative. There is a heavy weighting in the direction of disturbed behavior, the schizophrenic characteristic of abnormal seclusiveness being also pronounced. This is in sharp contrast to the situation prevailing at the immediate postoperative level. The group becomes relatively placid, as emphasized by the large "quiet and cooperative" block. No consistently disturbed behavior is obvious, nor does it appear at the subsequent periods that are represented. Again, the abnormally seclusive person predominates, the increase being readily explained on the basis of immediate postoperative lethargy and lassitude.

At the three and six month periods there is no gross increase in the incidence of the severely disturbed patient. The incidence of the intermittently disturbed

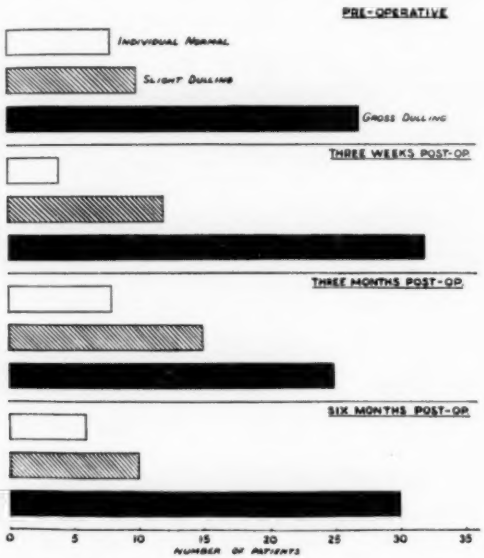

Chart 2.—Changes in affect in patients with chronic schizophrenia before and at stated intervals after prefrontal lobotomy.

patient has increased slightly. The same associability and abnormal seclusiveness stand out.

It is obvious, therefore, that up to the end of the six month postoperative period the reactivity of the group has been notably lessened. Consistently disturbed behavior has disappeared. The more notorious schizophrenic features remain relatively unchanged. Purely from the standpoint of management, a favorable balance has resulted.

The effect of the operation on the affective response of the patient is, of course, of the utmost importance. Lowering of the emotional tone is an implicit aim of the therapy. In schizophrenia, however, the situation is somewhat unique. With lobotomy, the affect is battered not only by the operation but by the psychosis

itself. Affective blunting, to a greater or less degree, is a fairly uniform concomitant of the disease, especially in its more chronic stages. However, even patients with little or no response to their environment can still react rather vigorously to such endogenous features as delusions and hallucinations.

Affective change as a result of the operation with our group is demonstrated in chart 2. It will be noted that gross dulling of affect overshadows each of the other categories at each observation period. The fact that this applies at the preoperative period must undoubtedly lead to the question whether such a group was a well chosen one for therapy in mind. It is suggested that this is a situation

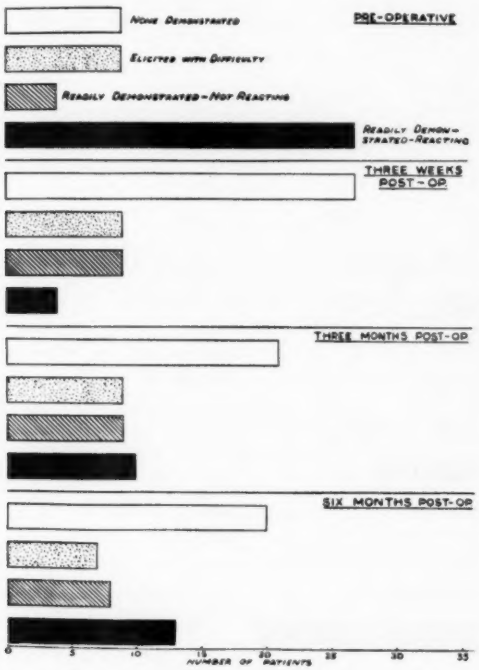

Chart 3.—Hallucinations in patients with chronic schizophrenia before and at stated intervals after prefrontal lobotomy.

which is inherent in such a group of chronic schizophrenics and must be so accepted. When the time levels are followed in sequence, it is seen that this characteristic remains essentially unchanged. If anything, it is slightly increased, again a possible reflection of the effects of organic interference.

Hallucinations and delusions (charts 3 and 4) are more clearly defined symptomatic entities. Furthermore, they are the commonest features of the disease, especially in its more chronic stages. Our series, as can be seen, is no exception.

Four descriptive categories have been used in the breakdown of the data on hallucinations (chart 3). The nonshaded block represents the patients in whom no

hallucinations could be demonstrated. There is a gradual ranging from this to the other extreme (solid block), which represents the patients who were strongly affected by their hallucinations and who reacted to them.

As might be anticipated, the latter type predominates at the preoperative level. This preponderance is further reenforced by four more patients, who, although not consistently reacting, are nevertheless vividly hallucinated.

At the three week postoperative stage an almost complete reversal of this situation occurs. The group in which no hallucinations can be demonstrated has increased to *27*, whereas the most traumatized group has decreased to four. The

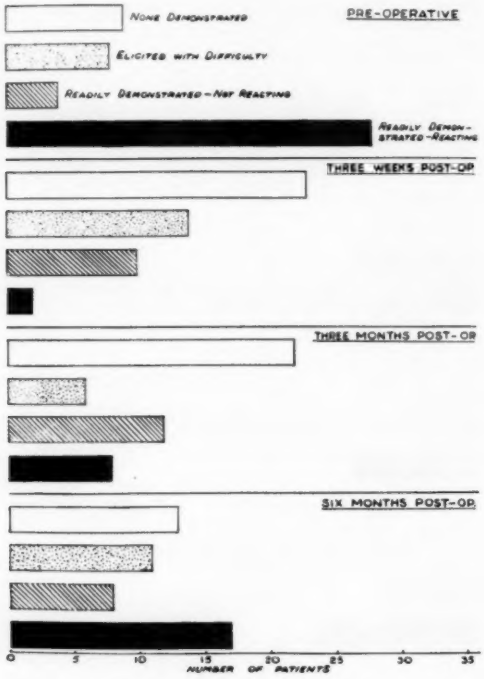

Chart 4.—Delusions in patients with chronic schizophrenia before and at stated intervals after prefrontal lobotomy.

two intermediate groups have increased slightly as a whole, but the most dramatic changes have occurred at the two extremes. It is obvious that considerable optimism, premature or otherwise, could be engendered by the picture presented at this time.

That this optimism would be somewhat premature is suggested when the situation at three and six months is examined. At the three month level there is evidence of a beginning trend toward more vivid hallucination. This trend continues at the six month period. At this stage there remains a substantially increased number of less traumatized patients.

The trend with reference to the delusional content of the group is evident in chart 4. The changes here rather closely parallel those demonstrated in chart 3. Again, a sharp change is noted at the three week postoperative period, followed by a gradual, but definite, trend in the direction of return to the preoperative state. With delusions the trend in the unfavorable direction is even more pronounced, and the favorable balance is slightly less.

In summarizing the trends indicated in the preceding discussion, it can be said that the changes, except that of affect, are on the whole in a favorable direction. One is left with a more placid, although still grossly blunted, group of patients, who are less traumatized by their symptoms. The unknown variable is the amount and duration of the organic overlay. For this reason, there arises the necessity for caution in prognosis. Even with the period under discussion there is evidence of regressive tendencies, most prominent from the three to the six month postoperative period. Whether this trend continues during subsequent months can only be determined as further observations are compiled. We feel justified in saying, however, that dogmatic predictions are rarely justified, at least prior to the three month postoperative time level.

II. VALUE OF CERTAIN POSSIBLE PROGNOSTIC CRITERIA

Along with clinical observations, these studies necessitated the compilation of data relative to age, length of illness and former treatment. We felt that organization of these data with respect to prognostic value would be worth while, even though the literature has dealt with this aspect repeatedly.

It has been stressed in most of the reported work that emotional tension, of greater or less degree, should be used as the basic criterion in planning a lobotomy. This applies whether the tension is in response to psychotic ideation or to intractable pain. The relief of this tension is, of course, implicit in the rationale of the operation. Other than this, however, there appears to be little uniform agreement as to what features should be used as a gage of future improvement. In regard to length of illness, Freeman and Watts [2] stated that the percentage of patients showing improvement is about the same whether the disability has existed for two years or for five years. The same authors [2] stated the belief that the younger the patient at the onset of his symptoms, the poorer is the prognosis. Again, Oltman and associates [7] stated that duration of illness is of little value as a criterion. These investigators found that there was a slight tendency toward poorer results in the younger age groups. They concluded, however, that this was due to the fact that the onset of relatively resistant forms of dementia precox is earlier than that of the other, more amenable, subgroups. As concerns response to previous therapy, Freeman and Watts [2] stated:

> If shock therapy gives a temporarily good result we are inclined to believe that lobotomy will give a prolonged good result. However, the fact that shock therapy fails does not mean that lobotomy will also fail.

One possible variable in the work that has been done pertaining to this aspect is the definition of improvement. It would appear to us that there is a wide scope for variation in this regard. In the present study, we have tried to be as conservative

7. Oltman, J. E.; Brody, B. S.; Friedman, S., and Green, W. J.: Frontal Lobotomy: Clinical Experiences with 107 Cases in a State Hospital, Am. J. Psychiat. **105**:742-751, 1949.

as possible. There is a certain proportion of the group who have shown a diminution in the intensity of their symptoms and whose behavior, although still bizarre, is somewhat less difficult than before operation. These patients could understandably be called improved. Yet the clinical dividing line between the preoperative and the postoperative condition of these patients is so slight that we felt it best to leave them in the category of unimproved patients. Improvement, as used in the present study, could be defined as follows: "General improvement in symptoms and behavior to the degree that [the patient] could live outside of hospital without experiencing gross difficulties in social adjustment." This, of course, does not necessarily mean that the persons who fall into this category are capable of supporting themselves or of getting along outside the hospital without supervision.

Again, we have attempted to show in graphic form the group breakdown in relation to these various factors. Chart 5 deals with the breakdown with

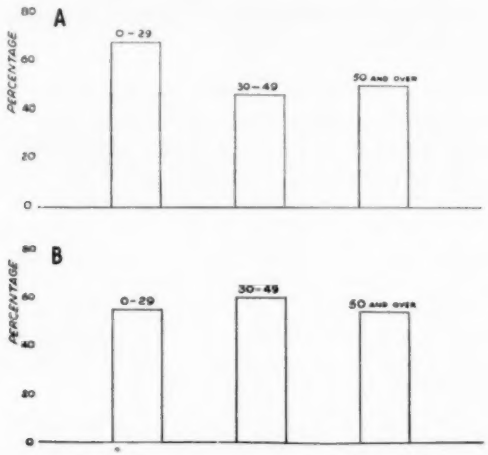

Chart 5.—Relation of improvement after prefrontal lobotomy (*A*) to number of electric shocks and (*B*) to number of insulin shock treatments necessary for stabilization.

respect to electric shock and insulin shock therapy. Each patient had received either insulin or electric shock treatment, the greater majority having had both. The various possible implications again come to mind in considering these factors. Should we anticipate a poorer result with lobotomy in the patient who has required an unusually large number of electric shocks to stabilize him? On the other hand, should a temporary good response to shock justify one in expecting a correspondingly good response to lobotomy?

In chart 5 *A* three categories are represented with respect to previous electric shock therapy. The numerical breakdown ranges from the group receiving no to 29 grand mal seizures to that receiving 50 or more. In each case only improvement in relation to each of these groups is shown. It will be noted that improvement is relatively higher in the group who received the least number of treatments. Statistically, however, the difference is not of real significance. We have gone

further and examined the 0 to 29 seizure group from the standpoint of status at the completion of shock therapy. We find that it is evenly divided as regards clinical improvement. With the present clinical group of limited size, therefore, we do not feel in any position to state that the patient's response to electric shock serves as a criterion for operative prognosis. Because of the suggestion of a possible trend, we intend to continue the investigation of this factor as the amount of clinical material increases.

In chart 5*B* there is a corresponding breakdown involving improvement in relation to previous insulin shock therapy. No trend is either obvious or suggested, and it appears that none could be anticipated with a larger group.

Chart 6*A* is concerned with improvement in relation to age. The age used here is that at the time of operation. Again, the percentage of improvement in relation to each of the age groups is shown. Although there is the suggestion of a trend

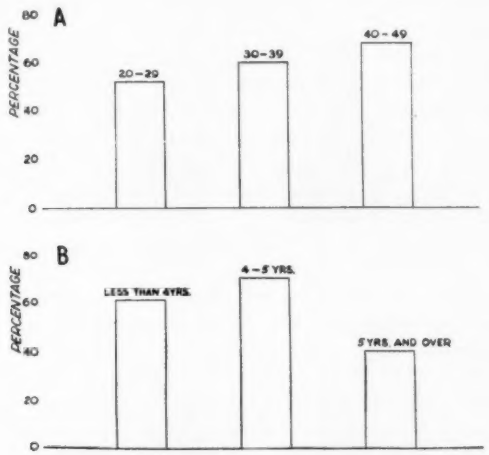

Chart 6.—Relation of improvement after prefrontal lobotomy (*A*) to age and (*B*) to duration of the schizophrenic illness.

toward greater improvement as the age of the group increases, statistically there is no significant difference. Again, the trend is not sufficiently pronounced to justify any predictions as to clearcut conclusions with a more sizable group.

Improvement in relation to length of illness is shown in chart 6*B*. A sharp drop in the percentage of improvement is noted in the group whose illnesses were of a duration of five years or more. This difference has been found to be on the borderline of statistical significance. Of the four criteria chosen for investigation, it appears that length of illness falls nearest to being of real value. In all probability, with an increase in the number of patients in the group investigated, the statistical significance of the difference represented in this graph will become real.

Therefore, although the analysis of these four factors does not yet represent any conclusive data, it is felt, nevertheless, that the trends suggested by the break-

downs in relation to electric shock therapy and length of illness are sufficiently pronounced to warrant further investigation. The latter, especially, appears to assume some significance.

III. GROUP TRENDS IN INTELLECTUAL FUNCTIONING

It has been pointed out more than once that an attempt to estimate the true intellectual capacity of a person with a long-standing psychosis involves many pitfalls and may be misleading. The blanketing effect of the psychosis almost invariably gives a distorted and untrue result. It is not the intention, therefore, in reporting this phase of our study, to suggest that the statistics used represent the native intelligence of the individual patients or of the group. With the data at hand, no attempt can be made to effect a comparison with the premorbid intellectual levels. Investigation now under way gives us some hope of being able to do this. Comparisons, therefore, not only will be preoperative and postoperative but will actually represent the functioning of the patient under various phases of psychotic intensity.

The matter of the effect of lobotomy on the intellectual functioning of the patient assumes rather large proportions in the minds of the relatives whose responsibility it is to give consent for operation. There are still those who express the apprehension that the patient will be reduced to the crude animal level. The studies reported in the literature give ample evidence for reassurance in this respect. This, of course, applies only to the standard technics and does not involve the more radical and posterior cuts.

It has consistently been reported that the intellectual functioning of the patient, as reflected by the standard tests, undergoes a decrease of varying degree during the more immediate postoperative period. Malmo,[8] utilizing forms I and II of the Wechsler-Bellevue Intelligence Scale, reported a loss of 1 to 16 points in five patients following lobotomy. The observation time covers a period of 41 to 83 days after operation. The results with the Wechsler-Bellevue test in the 107 cases from the Fairfield State Hospital [7] are summarized as showing a mild decrease in intellectual functioning during the early postoperative phase, followed by a restoration to a level equal to, or greater than, the preoperative status. In 31 cases in this series there was an average increase of 10 points on the Wechsler-Bellevue Scale six months after operation (Oltman, Brody, Friedman and Green [7]). From the standpoint of diagnostic makeup, the Fairfield series would appear to have certain clinical similarities to the group under discussion in this paper.

With the present clinical material, we have chosen the same time sequence as that used for the estimation of clinical changes, namely, before operation, and three weeks, three months and six months after operation. We anticipate that there will be a sufficiently large group available to permit us eventually to study the situation at the two year period.

For the purpose of estimating the intellectual functioning of this group, the results obtained from the application of the Wechsler-Bellevue Intelligence Scale have been used. As is well known, this test is so devised that the results are reported in the form of performance, verbal and full scale intelligence quotients.

8. Malmo, R. B.: Psychological Aspects of Frontal Gyrectomy and Frontal Lobotomy in Mental Patients, A. Research Nerv. & Ment. Dis., Proc. (1947) **27**:537-564, 1948.

The performance intelligence quotient is computed through scales designed to measure mental ability by tests of manipulation and assembly without language tests. For the verbal intelligence quotient, on the other hand, language tests are utilized and the test gives, in part at least, some reflection of abstract thinking. The full scale intelligence quotient gives an over-all estimate of the patient's level of intellectual functioning; although it is roughly the mean of the other two, it is not strictly so and is derived from previously computed tables.

It will be noted in the graphs which follow that the total group could not be tested at any one of the various time intervals. This was for various reasons. Prior to operation certain of the patients are too consistently inaccessible, disturbed or catatonic to allow testing to be done. This applies to some patients in the postoperative period also, but the major reason here is the discharge of the patient

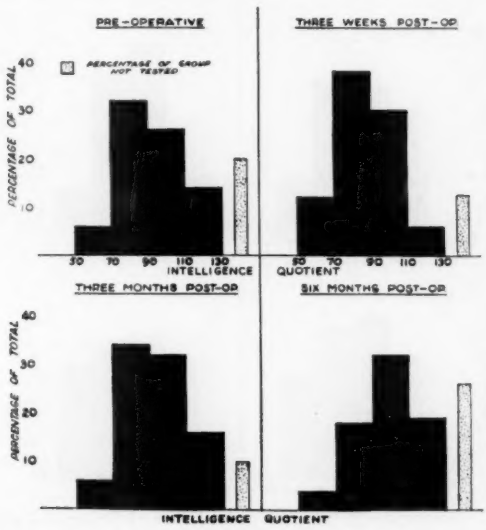

Chart 7.—Full scale intelligence quotients (Wechsler-Bellevue) before and at stated intervals after prefrontal lobotomy.

before the time for testing arrives. The possible significance of this in the over-all results will be noted more fully in discussion of the various graphs.

In chart 7 the full scale intelligence quotients for the group are represented at the various time intervals. In each case a range of 80 points is covered, this range being broken down into segments of 20. At no time did values for any of the group fall below the 50 level or rise above the 130 level. The value for each of the subgroups represented here is shown as a percentage of the total group. The stippled segments represent the percentage of the group which could not be tested. This is also shown as a percentage of the total group of 49 patients. At the preoperative level, as already mentioned, this is made up entirely of uncooperative and inaccessible patients. At the six month period, however, more than half this untested group is composed of patients who have been discharged and who have

shown a rising trend up to that time. The probability, therefore, is that if this additional number could have been tested, a reenforcement of the fractions of the group in the higher ranges of the scale would have resulted. It should also be pointed out that these represent the minimal percentage levels for each fraction. Any of the segments might be higher, but not lower.

A study of the situation at each period reveals that at the three week postoperative time level there tends to be a bunching in the middle and lower portions of the scale. There is obviously an increase in the number falling in the 50 to 90 range, the 110 to 130 segment being most markedly diminished. The efficiency of the group, therefore, as reflected by this means, is quite obviously diminished. It is well to keep in mind, however, that at this period the organic overlay is still

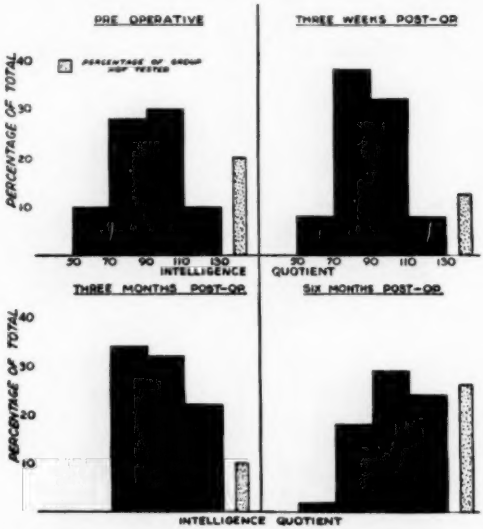

Chart 8.—Verbal intelligence quotients (Wechsler-Bellevue) before and at stated intervals after prefrontal lobotomy.

an important factor. At the three month period it appears that the situation is being rectified, the swing now being toward the upper portions of the scale both in the normal and in the superior area. At six months, even with the smaller number of patients tested, the improved showing in the higher ranges of the scale is maintained, and even improved, as far as the 110 to 130 segment is concerned. Even with the addition of the nontested portion of the group, it is fairly safe to assume that the group picture of intellectual functioning has not worsened as compared with the preoperative status but, to a slight degree at least, tends toward a better performance.

The trend suggested in relation to the full scale intelligence quotient is maintained with the performance section of the test (chart 8), but to an even more decided degree. Again, a tendency toward concentration in the middle and lower portions of the scale is demonstrated at the three week postoperative period. The

swing into the normal and superior levels, however, at three and six months is even more pronounced with the performance than with the full scale intelligence rating. As things stand, the 50 to 70 portion is practically eliminated, although this situation might not hold if values for the untested portion could be added. The most striking improvement is evidenced in the 110 to 130 segment, rising from a preoperative level of 10 per cent to a six months postoperative level of 24 per cent.

With the verbal intelligence quotient (chart 9) the relative improvement at the three and the six month postoperative period is again demonstrated, although here the trend is not so marked, and in some respects the situation is not up to the preoperative standard. This applies to the superior range, although this, again, might be raised to some degree if the data for the nontested portion of the group

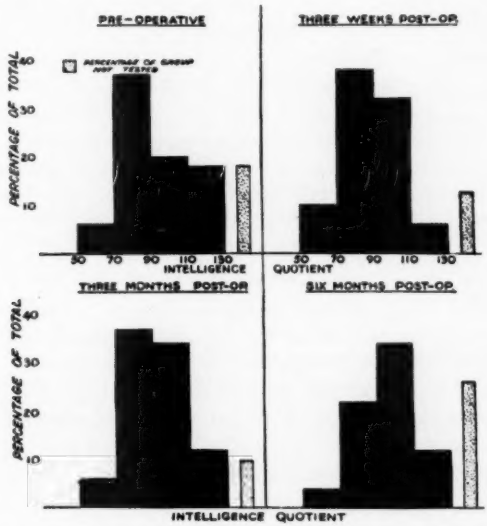

Chart 9.—Performance intelligence quotient (Wechsler-Bellevue) before and at stated intervals after prefrontal lobotomy.

could be added. Generally the trend is satisfactory, with the swing in the direction of normal, and away from the impaired side. Certainly, no relative worsening could be anticipated, even if the whole group had been tested.

Up to the six month postoperative period, therefore, the trend in intellectual functioning is generally a satisfactory one. From the standpoint of the group, there is no evidence of a lowering in the full scale, the verbal scale or the performance portions of the test used. On the contrary, there is a tendency toward improvement over the preoperative level. This is most marked on the portions of the test dealing with manipulation and assembly, and not involving language or abstract thinking. Again, it is emphasized that this is a relative, and not an absolute, improvement. The most logical explanation, in view of the clinical

findings already discussed, is that this improvement is in great part due to elimination of the inhibiting influence of the psychosis.

The very pronounced improvement shown on the performance portions of the test leads to some practical conjectures. Reasonably, it would suggest that these patients should do best in occupations of a manual or manipulative type, in preference to work in which more abstract reasoning is of importance. From our experience with them as individuals this appears to be generally the case. Unfortunately, however, the organic nature of the treatment frequently leaves a certain inability in application and concentration. As a result, we find ourselves in many cases faced with a paradox, which forms an obstacle to rehabilitation. Although the operation frees the patient from his psychosis to the degree that he performs better along manual and practical lines, it also leaves him with the inability to concentrate sufficiently to utilize this asset.

SUMMARY

Certain preliminary studies carried out on a group of 49 chronic schizophrenic patients who had undergone prefrontal lobotomy are reported. The present report covers the period up to six months after operation. The investigations which form the material of this paper include a study of symptomatic trends, the evaluation of certain possible clinical criteria for operation and the demonstration of trends in intellectual functioning, as reflected by results of the Wechsler-Bellevue Intelligence Scale.

CONCLUSIONS

1. In this group, the changes occurring as a result of lobotomy within the six month postoperative period involve mainly diminution in the intensity of the symptoms and improvement in behavior. The basic schizophrenic nature of the patients does not appear to be greatly altered.

2. Predictions as to the eventual outcome should be made with caution within the six month postoperative period. Relapses and exacerbations of symptoms are not infrequent within this period.

3. Factors such as age and reaction to previous treatment show little promise of being of any value as prognostic criteria. Length of psychosis, however, does appear significant, illnesses of over five years reacting less favorably to the treatment.

4. There is no indication that the intellectual functioning of the patient with chronic schizophrenia is adversely affected up to the six month postoperative time level. On the contrary, there is a general rise above the preoperative level, this being most pronounced in the sphere of performance.

Abstracts from Current Literature

Physiology and Biochemistry

PHYSIOLOGICAL DETERMINATION OF THE BOUNDARY OF THE ACOUSTIC AREA IN THE CEREBRAL CORTEX OF THE DOG. A. R. Tunturi, Am. J. Physiol. **160**:395 (Feb.) 1950.

Tunturi devised a method for determination of the boundary of the acoustic area in the cerebral cortex of the dog by the application of strychnine locally to the cortex and stimulation with sound. The appearance of an induced strychnine spike was used to indicate the existence of an afferent convection. It was found that the acoustic area was bounded by the suprasylvian and ectosylvian sulci. Anteriorly the boundary was a line across the dorsal end of the anterior ectosylvian gyrus. Ventrally the area was limited by the junction of the posterior ectosylvian and the composite gyrus. The middle ectosylvian gyrus was characterized by a specific arrangement of the responses with respect to frequencies, lowest thresholds and consistency of responses. This area has been termed tentatively the primary projection area. On the dorsal end of the anterior ectosylvian gyrus there exists a small discrete area for low frequencies, not activated at usual levels by high frequency tones. It does not extend across the sylvian gyrus. The posterior ectosylvian gyrus is distinct physiologically from both this anterior area and the area of the middle ectosylvian gyrus. The third area is a 2 by 2 mm. region, isolated from the remainder of the acoustic cortex.

ALPERS, Philadelphia.

SPONTANEOUS ELECTRICAL ACTIVITY OF THE HUMAN THALAMUS. D. WILLIAMS and G. PARSONS-SMITH, Brain **72**: 450, 1950.

Williams and Parsons-Smith investigated the spontaneous activity of the thalamus by means of bipolar recordings between serial pairs of electrodes enclosed in a brain needle; the brain needle was inserted according to the technic used for ventriculography. Simultaneous recordings were made of the electrical activity of the surface gray matter, the basal gray matter, particularly the thalamus, and the intervening white matter; scalp electrodes were also used.

Twenty-one subjects were studied; the conditions affecting these patients were brain tumor, grand mal epilepsy and cortical atrophy. In most cases, Williams and Parsons-Smith found the thalamogram to be featureless, without constant or characteristic rhythm, whatever might be occurring in the electroencephalogram. In a small proportion of abnormal subjects, short bursts of 16 to 22 cycles per second rhythms arose in the thalamus. One half to two per second waves might occur when deep-seated tumors invaded the thalamus. In patients with organic cerebral damage there was no apparent relation between the spontaneous rhythms seen in the thalamus and the spontaneous rhythm of the cortex. Cortical and thalamic rhythms apparently are independent of each other.

FRENKEL, Philadelphia.

Neuropathology

MASSIVE SPONTANEOUS HEMORRHAGE IN GLIOMAS: A REPORT OF SEVEN VERIFIED CASES. L. O. J. MANGANIELLO, J. Nerv. & Ment. Dis. **110**:277 (Oct.) 1949.

Manganiello reports the clinical and pathological features of seven cases of massive spontaneous hemorrhage in gliomas occurring in a series of 183 gliomas. He stresses the clinical importance of focal, progressive neurological signs and symptoms antedating the symptoms of hemorrhage as a point of differential diagnosis when primary vascular hemorrhage is considered. Of the 183 gliomas, 3.8 per cent produced this syndrome of massive spontaneous hemorrhage, and spongioblastoma multiforme comprised 43 per cent of the tumors with massive hemorrhage. The author subscribes to the view that intracerebral hemorrhage is preceded by softening of the brain tissue, which thereby deprives a vessel wall of support at a focal point.

FARMER, Philadelphia.

EPENDYMOMAS AND CHOROID PLEXUS PAPILLOMAS. NILS RINGERTZ and ALFRED RAYMOND, J. Neuropath. & Experimental Neurol. **8**:355 (Oct.) 1949.

This paper is a record of observations on the pathological anatomy in a series of 72 cases of ependymoma and 11 cases of papilloma of the choroid plexus.

The authors feel that the division of ependymomas into two distinct forms is fully supported by this analysis and should be maintained. The classification of ependymomas and choroid papillomas into three subgroups, namely, cellular, papillary and epithelial, may be justifiable from a descriptive point of view but is not in accord with biological considerations.

The view of some investigators (Kernohan and co-workers) that ependymomas (epithelial, cellular and papillary), containing a few epithelial formations, have a more favorable prognosis than tumors of strictly cellular or papillary structure is not substantiated by the observations of Ringertz and Raymond.

The authors conclude that, in spite of their common origin, ependymomas and choroidal papillomas present important differences in histological structure and biological characteristics, making it necessary to consider them as two distinct types of tumor. In each of these groups are to be found benign, as well as malignant, tumors, called, respectively, ependymoma and malignant ependymoma, and papilloma and epithelioma choroideum.

ALPERS, Philadelphia.

CYTOCHROME AND CYTOCHROME OXIDASE IN MULTIPLE SCLEROSIS. I. HUSZÁK, Confinia neurol. **10**:104, 1949.

Huszák refers to previous work in which he demonstrated that in the gray matter of nerve tissue there is found an iron-containing, oxygen-activating and oxygen carrier system, the so-called Warburg-Keilin system. This system appears to be absent in the white matter. He refers also to his previous work which demonstrated the likelihood that oxygen activation in the white matter occurs with the help of a copper protein.

Cytochrome oxidase, or indophenol oxidase, is determined colorimetrically by exposing brain slices to the "Nadi reagent" (alpha naphthol and dimethyl-para-phenylenediamine), which turns the tissue blue when this enzyme is present. Normally this reaction takes place only in gray matter. Slices of nerve tissue from a patient who died of multiple sclerosis were examined by this technic. The cytochromes were determined spectroscopically.

The sclerotic plaques of multiple sclerosis turned blue in the Nadi reagent simultaneously with the gray matter; the intensity of the reaction of the plaques was at first the same but progressively became greater than that of the gray matter. A faint absorption line characteristic of cytochromes appeared in the plaques. Its maximum lay at 550 millimicrons, suggesting that the substance was cytochrome C.

Huszák argues that since the reaction is thermolabile, the substance concerned must be in the nature of an enzyme. He considers it possible that the cytochrome and the cytochrome oxidase are carried into the plaques with the phagocytic or glial elements. He concludes that it is probable that these substances play a part in those oxidation processes which effect destruction and repair in damaged nerve tissue.

FOLEY, Boston.

Psychiatry and Psychopathology

THE CONCEPT OF TRANSFERENCE. W. V. SILVERBERG, Psychoanalyt. Quart. **17**:303 (July) 1948.

Silverberg defines transference as a repetitious attempt to rectify in action a traumatic situation which, though it is in a sense "remembered," cannot be recalled; it is the attempt to learn by a series of rehearsals how not to be helpless or powerless in a situation which originally found one so, the original situation being "remembered," although not consciously recalled. The author points out, first, that transference defined in this way cannot be confined to psychoanalytic psychotherapy, and, second, that any human behavior which is not of this nature is not transference. Thus, transference is a dynamism that may occur within a relationship and cannot constitute an entire relationship. Clinically, transference may be detected

by two qualities which are always present: It is always irrational, no matter how well it may be rationalized, and it is always subjectively disagreeable to the persons experiencing it. Every transference indicates a need to exert complete control over external circumstances—in particular, human and social ones.

WERMUTH, Philadelphia.

THE EQUIVALENTS OF MATRICIDE. R. M. LINDNER, Psychoanalyt. Quart. **17**:453 (Oct.) 1948.

Lindner points out that matricide is perhaps the rarest and most abhorred of crimes. As strong as the love for the mother is the fear that she inspires and the hostility which she evokes. The author describes through the case material the various matricidal equivalents which may occur in murder, in suicide, in acting out and in dreams. Certain defense mechanisms permit matricidal equivalents by giving expression in a variety of ways to the repressed wish, allowing discharge of varying quantities of anxiety insufficient to overwhelm the ego and preventing the fantasy from emerging undisguised. The most effective defenses against matricide are displacement, reaction formation, projection, repression, introjection and identification.

WERMUTH, Philadelphia.

A CASE OF PATHOLOGICAL JEALOUSY. G. BARAG, Psychoanalyt. Quart. **18**:1 (Jan.) 1949.

Barag reports the analysis of a man aged 33 who was living in Israel. The patient had been married 10 years and had a 9 year old son. His wife was his first serious attachment, and the first woman with whom he had had vaginal intercourse. There had been countless other sexual relationships, both prior to and following the marriage. During these, only *ejaculatio ante portas* had occurred. Shortly before analysis began, the patient became extremely jealous of other men in whom he believed his wife was showing interest. The extent of his jealousy became so unbearable that he was referred to psychoanalytic treatment.

The patient was reared in an environment of strong sexual tensions. He slept for many years in his parents' bedroom. He witnessed the primal scene repeatedly and interpreted it sadistically. He began to hate his previously adored father and to fear him, while admiring his male strength. He feared his mother because he believed she took his father's penis away and might keep and destroy it. These observations led him to develop an intense fear of castration at the height of his phallic narcissism. Nothing was as precious to him as his penis, and whatever he loved, he loved as he did his penis. Thus he came to identify his mother with his penis. In wooing his mother, he felt defeated by his father and abandoned by his mother. He attempted in fantasy to take her child, his younger brother, away from her and to incorporate it in himself but desisted because the thought of being a woman was too fearsome. He suppressed his inimical strivings and used this younger brother, and other boys, as love objects in a partial identification with his mother, but in an active, phallic, aggressive manner. While consciously retaining the oedipal hate for his father, he directed unconscious, passive love desires toward him and a substitute, Wassja, who represented the pre-oedipal attachment to his father. His heterosexual strivings became stronger during puberty, encouraged by the easy accessibility of female objects; but during his mother's lifetime he had no significant attachment, only fleeting love adventures with extragenital sex acts. After her death he sought his mother in the person of his wife, embarked on the founding of a family, and genital relations were established. The process, however, was not complete; his genital potency was impaired, and he continued the pursuit of fleeting narcissistic relationships.

Doubtless it was of exogamic significance that he, an oriental Jew, had taken for a wife a woman from a Sephardic community. As long as his wife did not complain, he felt well; but, having reason for dissatisfaction, she made him feel responsible for it. This aroused dormant feelings of guilt, which stemmed from his thieving infantile impulses toward his pregnant mother, and released from repression the unresolved aggression and disappointment which he had experienced in the oedipal conflict. In accordance with the repetition compulsion, he withdrew his libido from her and again directed it toward homosexual objects, images of his father. Unconsciously, he approached the male objects through his wife, in a partial feminine identification with her. He defended himself against his homosexual strivings by the

mechanism of projection. He accused her of trying to seduce the men. His wife protested; worse and worse scenes ensued, and the situation became unbearable. He could not work because the relationship with his comrades was for him also sexualized. He sank into depression, blamed his wife for this miserable state of affairs; and it was in this condition that he sought treatment.

He proved to be an excellent subject for psychoanalysis because of the unusual accessibility of his unconscious, the preservation of reality testing and the readiness with which he effected a positive transference. The combination of phallic narcissism with partial feminine object choice permitted him to maintain good contact with the outer world, to be capable of transference and to complete an analysis. The treatment was completed in less than a year. The therapeutic result was immediate and thoroughly satisfying. He was fully potent, in love only with his wife, mature and felt self assured with his comrades. At the time of the report, more than a year later, he remained completely healthy and secure, and he had, in the meantime, become the father of a second child.

WERMUTH, Philadelphia.

PREFRONTAL LEUKOTOMY. B. HORANYI, Monatsschr. f. Psychiat. u. Neurol. **118**:105 (Aug.) 1949.

Horanyi discusses 42 cases in which prefrontal leukotomy was performed for relief either of psychosis or of pain. He found that incisions made rostral to the plane of the coronal suture yielded good results in cases of catatonic stupor. Incisions caudal to that plane produced undesirable complications, as Freeman and Watts had observed. Horanyi believes it necessary to cut only the lower quadrants of the frontal lobes to eliminate the emotion accompanying delusions and hallucinations. The contention that section of the orbitotemporal fibers leads to extroversion and increased motor activities could not be verified. A leukotomy performed on a negativistic, stuporous patient was followed by an immediate increase in speech and motility with a hypomanic coloring, extroversion and improved emotional tone. Eight days after operation the patient died suddenly of acute heart failure. Sections of the temporal lobe disclosed no degeneration. The author surmises that the section of the frontohypothalamic fibers resulted in a change from autism to extroversion, inasmuch as the frontothalamic fibers were uninjured. Horanyi claims that the section of the frontothalamic pathways, in particular, is not necessary for improvement in schizophrenia and depression, for improvement may also occur in these conditions after head trauma and in the presence of a cerebral tumor. The personality changes following leukotomy, such as changes in spontaneity, vital intensity, approach to the world, personal ambitions and the individual qualities of the emotional life, may be found in any disease localized to the frontal lobe. In other words, there is no structure of the white matter of the frontal lobe which should be cut to obtain specific mental reactions. Although Horanyi has not performed any topectomies, he has experimented with contact irradiation of exposed circumscribed areas of the cortex to achieve the same effect.

In five patients with metastatic carcinoma and severe pain, there was dramatic relief after leukotomy. Pain was relieved when the section occurred in the Freeman-Watts plane, as well as when it was oral or caudal to it. The reaction to pinprick persisted, although the patient had been relieved of other existent pain. In experiments on patients with leukotomy, solutions producing burning pain were introduced into the urinary bladder. Patients on whom leukotomy had been performed because of pain did not perceive vesical pain, whereas those operated on because of psychotic states experienced intense vesical pain. Other sensory modalities were not affected by leukotomy, and the emotional reaction to itching, tickling and stroking was not affected.

The patient can experience pain after leukotomy, but its psychical realization, as well as the emotional reaction to it, disappears. It is suggested that the emotions accompanying pain in humans tend to migrate from the thalamic-hypothalamic region toward the more rostral portions of the cortex, following the principle of progressive cortical dominance. The affect accompanying pain may be the result of a simultaneous cortical action and the interaction of the thalamic-hypothalamic and frontal regions. Histological studies of the frontal cortex did not disclose any remarkable cellular alteration, and the electroencephalograms did not exhibit

significant changes in those cases in which leukotomy had been performed because of pain. A suspension of cortical function cannot be held responsible for the absence of the affect accompanying pain. The thalamus and postcentral gyrus produce elementary somatic pain, whereas the thalamofrontal system produces to some extent "humanized" pain affects. There has been a greater corticalization of the emotions accompanying the more archaic visceral pain than of the emotions of pain derived from the skin. Pain may return after leukotomy.

In many patients it was noted that the affective concomitants of hallucinations and delusions subsided after leukotomy. This effect was often transitory, and many patients became aggressive again after the operation. The author relates this circumstance to the fact that leukotomy interrupts the frontosubcortical fibers and, to a less degree, the corticocortical fibers. He supposes that emotions represent the products of the frontothalamic system and that the emotional reaction is corticosubcortical, whereas thought may possibly be a purely cortical function. He also concludes that delusions are not the result of affect. It is believed that there exists a primary alteration in the emotional life and the delusion appears as a result of this alteration. After leukotomy the delusions may persist, but the accompanying affect may disappear. Horanyi deems it improbable that the emotions play a pivotal role in the genesis of delusions. It was also observed that the affect related to hallucinations is abolished by leukotomy. It is probable that visual hallucinations arise in the occipital cortex and auditory hallucinations in the first temporal gyrus. Nonetheless, it is interesting that the affect is removed by leukotomy. This may be related to the fact that in every psychic act the cortex operates as a whole and is dependent on the intactness of the frontothalamic connections. Another conclusion reached from this study is that anxiety of any origin is eliminated by leukotomy and that this type of operation is indicated for severe, intractable anxiety. The somatic manifestations of anxiety are related to changes in the hypothalamicohypophysial system, and the cortex may exert an inhibiting influence on the anxiety-producing function of this system. Anxiety is also conceived as having two components: a vegetative, connected with the hypothalamus, and a psychic, which is the function of the frontothalamic system. The results obtained from leukotomy would seem to indicate that many emotions represent the interaction of the frontothalamic-hypothalamic system. The personality as a whole is affected by leukotomy in the sense that the patients are simpler and more adaptable; their interests and demands of life are restricted, and they lose their drive for perfection. They assume an easier-going attitude to life, and they exhibit a lack of activity. Horanyi found that individual characteristics seemed to disappear, the personal reactive tendencies were lost and the patients seemed to react more uniformly. Stimuli from the environment could not easily mobilize their emotions. There was also striking indifference to time as related to the future. Horanyi considers this alteration in *Zeiterbnis* a characteristic of frontal lobe dysfunction following leukotomy. After leukotomy patients with metastatic carcinoma exhibited little concern over death, although it was imminent.

Horanyi suggests three indications for leukotomy: (1) Intractable pain produced by any disease. (2) Highly emotional tension when it makes life intolerable for others because of aggressions due to hallucinations or delusions, or because of the aggressive tendencies of epileptics; or when life becomes intolerable to the patient because of anxiety associated with depressive or obsessive states or because of the primary anxiety in schizophrenia. (3) Changes in primary activity, such as those in catatonic agitation or in catatonic stupor and depressive states if they are not intractable.

PISETSKY, New York.

INFLUENCE ON A PERIODIC PSYCHOSIS OF HEMATOLOGICAL AND BIOCHEMICAL ALTERATIONS. N. SPEIJER, Monatsschr. f. Psychiat. u. Neurol. **118**:69 (Aug.) 1949.

Speijer reports the case of a man aged 45 with a periodically recurring psychosis and coincidental changes in the blood count and blood chemistry. The patient's illness had its onset at the age of 16, when he was hospitalized for a "hysterical" condition, lasting six weeks. Later that year he was treated again because he was influenced by rays and was excited. The diagnosis of dementia precox was made. At later periods of hospitalization, he was designated as having the degenerative form of manic-depressive psychosis. Between psychotic episodes he was entirely normal. The author, who studied the patient daily for three years, observed

15 psychotic episodes. Shortly before becoming psychotic, the patient would complain of insomnia; he would become incoherent and gradually confusion, excitement and aggressive behavior would develop. The level of consciousness also sank. After a few days the patient became quieter, and he gradually adopted normal behavior. After a lapse of about two months, the psychosis reappeared, with a similar picture.

Daily blood counts showed no variation in the white cell count, but there were deviations in the erythrocyte count. During his normal period, his red cell count averaged 5,000,000, when he became psychotic, the count dropped to about 4,000,000 cells and rose again as the psychosis subsided. The number of red blood cells paralleled the state of the psychosis during all the abnormal phases. The hemoglobin and hematocrit readings fluctuated with the number of red blood cells. There was no alteration in erythrocyte fragility, and the results of the van den Bergh tests and the hepatic function and glucose tolerance tests were normal. Chloride values fluctuated, but there was no direct correlation with the psychosis. During a psychotic episode the blood calcium rose to 11 or 12 mg. per 100 cc., whereas normal values varied from 9 to 10 mg. per 100 cc. The calcium value returned to normal before the red cell count. The phosphorus curve was the reverse of the calcium curve when the daily values were plotted. The values for alkaline phosphatase were not remarkable.

The low calcium diet of Snapper was tried. It was observed that if the patient was maintained on a small amount of calcium the psychosis could be prevented. Low calcium diets were administered 14 days before the psychotic episode was expected, and if the patient was kept on 56 mg. of calcium a day the psychosis lasted only nine days, instead of many weeks, and was less severe.

PISETSKY, New York.

Meninges and Blood Vessels

ACUTE PORPHYRIA WITH SPINAL FLUID CHANGES. H. A. LYONS, Ann. Int. Med. **33**:711 (Sept.) 1950.

Of cases of porphyria with neurological signs, not a single case has been reported with abnormalities in the spinal fluid. Lyons reports a case of acute idiopathic porphyria occurring in a white man aged 27 with abnormalities of the spinal fluid. He believes that these changes were due to the abnormal porphyrins affecting the meninges; however, other possibilities are mentioned. Urinalysis in this case revealed porphyrins. Unfortunately, the spinal fluid was not examined for the presence of porphyrins.

ALPERS, Philadelphia.

LOSS OF SPEECH DUE TO MENINGITIC DEAFNESS. CHARLES E. KINNEY, Arch. Otolaryng. **47**:303 (March) 1948.

From a careful study of 29 cases of total deafness due to meningitis, with subsequent loss of speech, Kinney concludes that when a person with normal hearing and normal speech becomes totally deaf he tends to lose his speech to an extent directly proportional to the length of time that he has had speech. Therefore, speech training must be begun promptly, especially in younger patients whose memory patterns are not yet firmly established. The lapse of time between recovery from meningitis and the onset of loss of speech increases in proportion to the age at which the deafness occurs. A survey of the causative organisms in these cases indicated that meningococcic meningitis is more likely to produce total deafness than meningitis caused by other types of bacteria.

An interesting observation was the discovery that children who had lost all other hearing sensations could appreciate the sound of a flying two motor airplane. Further investigation of this fact will be made, with the hope that new methods of speech training for deaf children may be developed.

RYAN, Philadelphia.

ARTERIOVENOUS ANEURYSM OF THE INTERNAL CAROTID ARTERY IN THE CAVERNOUS SINUS. L. M. FREEDMAN, Arch. Otolaryng. **52**:351 (Sept.) 1950.

Freedman reports a spontaneous arteriovenous aneurysm of the internal carotid artery in the right cavernous sinus, occurring in a woman of early middle age who gave a family history of aneurysm. She had advanced arteriosclerosis. The first symptom was a sense of

pulsation anterior to the right auricle, which was mentioned only incidentally and had been going on for several weeks when she was seen for consideration of polypoid ethmoiditis. For reasons unrelated to her condition, the ethmoidectomy was delayed for two months, during which pulsating exophthalmos, bruit and swishing sounds supervened. It was then possible to make the diagnosis, which might have been obscured by the ethmoidectomy and might have raised the question whether the cause of the arteriovenous aneurysm was not in some way related to the operation. Eventually the bilateral ethmoidectomy was carried out, with successful results.

A few weeks later, when the exophthalmos became more prominent, ligation of the common carotid artery was carried out. There was a fleeting reaction, with slight facial paralysis and partial hemiplegia, lasting six to eight hours. The eye then receded to its normal position, and all symptoms disappeared within one week.

ALPERS, Philadelphia.

REMISSION AS A FEATURE OF TORULOSIS. H. N. WILLARD and H. G. WOLFF, J. NERV. & Ment. Dis. **112**:237 (Sept.) 1950.

Most patients who contract torulosis die within six months. If they survive the acute phase, they live from two to four years, despite the evidence of active infection. The authors report the case of a pharmacist employed in penicillin research, who began to have irritability and anorexia in April 1945. The symptoms progressed insidiously, so that by September 1945 he had periods of confusion, fever, pain over the right eye, slight cervical rigidity and urinary retention. The spinal fluid contained 144 white cells per cubic millimeter with 97 per cent lymphocytes. The count rose to 336 cells per cubic millimeter one month later. The patient gradually improved so that he was able to pursue his research from January 1946 to September 1947, despite mild elevations in temperature in the evening. After September 1947 there gradually developed headaches, mental confusion, weakness of the lower extremities, shuffling gait and urinary incontinence. The spinal fluid contained 199 cells per cubic millimeter, with 97 per cent lymphocytes, and Torula histolytica was cultured from the fluid. He died in November 1947, and necropsy revealed torula meningitis.

BERLIN, Chicago.

LEPTOSPIRAL DISEASES WITH ASPECTS OF SO-CALLED IDIOPATHIC AND ABACTERIAL MENINGITIS. W. SCHEID, Deutsche med. Wchnschr. **74**:898 (July 29) 1949.

Scheid points out that Wallgren, in 1925, described a form of meningitis which he identified as acute aseptic meningitis. Subsequent reports by numerous other investigators frequently designated this process as benign lymphocytic meningitis. Scheid believes that the terms "aseptic" and "abacterial" can be misleading, because the terms indicate only that no organism can be detected with the customary microscopic and cultural methods. Aseptic, or abacterial, meningitis is really not an entity but a syndrome that may have various causes. In some cases, epidemiological considerations may indicate a poliomyelitic process. The virus of epidemic parotitis likewise may cause meningitis, and in some cases the typical symptom of parotitis is absent. Infectious mononucleosis also has been known to be associated with symptoms of abacterial meningitis. The author cites cases which demonstrate that leptospiral infection may present features of abacterial meningitis. Serologic studies indicated infection with Leptospira canicola or with Leptospira icterohaemorrhagiae, and epidemiological inquiries disclosed contact with diseased dogs. Contradictory statements regarding the frequency of meningitic symptoms in leptospiral infections are probably largely due to the fact that examinations of the cerebrospinal fluid were not done. The assumption that the meningitic form of leptospirosis represents a special complication cannot be defended. It is more probable that, as in syphilis, there is frequently, if not regularly, an infection of the meninges, which is not necessarily reflected in the cerebrospinal fluid. Changes in the cerebrospinal fluid may persist long after other meningitic symptoms have subsided. The sedimentation reaction suggests that leptospiras may persist in various organs, including the meninges. The meningitic disturbances produced by leptospiral organisms are frequently atypical, and only serologic studies can verify the diagnosis. The possibility of a leptospiral infection should be taken into consideration in all cases of abacterial meningitis.

J. A. M. A.

ARTERIOVENOUS ANEURYSMS IN BRAIN. H. OLIVECRONA, Nord. Med. **41**:843 (May 13) 1949.

Olivecrona states that in patients with epileptic attacks, especially of the jacksonian type, and a history of one or several subarachnoid hemorrhages, the diagnosis of arteriovenous aneurysm is practically certain. A systolic blowing sound is pathognomonic but is a relatively rare symptom. Arteriovenous aneurysms may be suspected in other conditions, particularly subarachnoid and intracerebral hemorrhages in younger persons without hypertension. Arteriography is always indicated when arteriovenous aneurysm is suspected. In treatment the choice lies between removal of the aneurysm and leaving it alone. Experiences with ligature of the carotid artery were discouraging. The aneurysm was extirpated in 47 of the 79 patients treated in the neurosurgical division of the Serafimer Hospital from 1923 to 1948, with an operative mortality of 8.5 per cent. The aneurysm was removed from 24 of the 42 patients treated from 1936 and from 18 of the 19 treated from 1946 to 1948. Arteriovenous aneurysms may be inoperable because of the site, as in the case of most aneurysms in the posterior fissure and all located in the brain stem, or because of their size. Late results show eight of the 24 patients operated on from 1936 to 1946 are well, with full or almost full ability to work. Eight who had defects that in several cases were present before operation but in some instances were aggravated, are partially able to work; the remaining five survivors are invalids. In the case of epilepsy the prognosis is best in younger patients with short anamneses; it is unfavorable in inveterate cases.

J. A. M. A.

Diseases of the Brain

THE FAMILIAL OCCURRENCE OF MULTIPLE SCLEROSIS AND ITS IMPLICATIONS. R. P. MACKAY, Ann. Int. Med. **33**:298 (Aug.) 1950.

This study is a review of the entire question of the familial occurrence of multiple sclerosis, with the detailed report of five instances of familial multiple sclerosis from the author's private practice. The available medical literature has been reviewed for reports of familial multiple sclerosis and a table compiled of the acceptable cases reported through 1948. These number 79 family groups, with an aggregate of 177 patients. The addition of the author's five families bring the totals to 84 family groups and 188 affected persons.

The precise question to be answered is whether the incidence of familial multiple sclerosis is greater than the incidence of the disease in general population. Curtius and his school attacked this problem by the laborious but direct method of studying the relatives of patients with multiple sclerosis and comparing the incidence of the disease among them with that in the general population. They found that the incidence of multiple sclerosis was five times as great among the total relatives and twenty times as great among the siblings of their German sclerotic patients as the incidence among the general Swiss population. There is no evidence that contagion explains the familial occurrence of multiple sclerosis.

Mackey believes that the currently available incidence strongly suggests that multiple sclerosis exhibits a familial incidence more frequently than mere chance would determine. On the other hand, the disease is too often nonfamilial for a familial, constitutional factor to be its sole cause. He postulates the following theory: 1. There is a familial, constitutional *Bereitschaft*, or vulnerability, to multiple sclerosis. This vulnerability, possibly nonessential and nonspecific, is subclinical and in itself is inadequate to produce the disease. 2. There is a second, nonfamilial, possibly exogenous cause or group of causes which is competent to evoke the disease, especially when the first, or constitutional, factor is already present.

ALPERS, Philadelphia.

BRAIN ABSCESS AND CONGENITAL HEART DISEASE. R. F. MARONDE, Ann. Int. Med. **33**:602 (Sept.) 1950.

Maronde studied the autopsy incidence of brain abscess associated with congenital cardiovascular shunts, not including patent ductus arteriosus. Eleven acceptable cases of this syndrome were found in a series of 13,883 autopsies performed in a 10 year period. These 11 cases were of persons over 2 yeaers of age at the time of death.

There were 81 cases in the same age group with autopsy evidence of the cardiovascular shunts under study. Of these 11 acceptable cases, brain abscess was associated with ventricular and auricular defects in 2, with ventricular and auricular septum defects, together with a rudimentary right ventricle, in 1 and with an isolated ventricular septum defect in 4.

ALPERS, Philadelphia.

ABSCESS OF THE CEREBELLAR LOBE OF OTOGENIC ORIGIN. JOSEPH S. MEDWICK, ALFRED UIHLEIN and OLAV E. HALLBERG, Arch. Otolaryng. **50**:429 (Oct.) 1949.

Cerebellar abscess of otogenic origin is rare. Chronic suppurative otitis media is generally considered the chief causative agent in cerebellar abscess formation, but such abscesses have also been reported secondary to acute otitis media. Six cases are presented in four of which recovery followed chemotherapy and surgical intervention. Early diagnosis, followed by adequate surgical treatment and supported by administration of the sulfonamide drugs and penicillin, will greatly reduce the morbidity and mortality resulting from cerebellar abscess secondary to otitis media.

RYAN, Philadelphia.

ABSCESS OF THE BRAIN FOLLOWING TONSILLECTOMY AND ADENOIDECTOMY. SAMUEL A. ALEXANDER and ROYAL REYNOLDS, Arch. Otolaryng. **50**:450 (Oct.) 1949.

Although tonsils and adenoids are frequently the source of infection and the tonsillar and postnasal spaces are often traumatized during tonsillectomy and adenoidectomy, cerebral complications are extremely rare. A case is reported in which cerebral abscess developed five days after tonsillectomy and adenoidectomy. A diagnosis of poliomyelitis was held until autopsy revealed an abscess of the left frontal lobe. This case suggests the possibility that in other cases the diagnosis of poliomyelitis following tonsillectomy and adenoidectomy may have been in error.

RYAN, Philadelphia.

ALLERGY AS A CAUSE OF NUCHAL MYALGIA AND ASSOCIATED HEADACHE. THERON G. RANDOLPH, Arch. Otolaryng. **50**:745 (Dec.) 1949.

Myalgia of the posterior cervical muscles has been attributed to a number of etiological agents and designated by various terms, such as tension headache and fibrositis. Not until 1931 was this type of pain considered as a type of allergic response.

In the observations made on patients undergoing food allergy tests, the frequent occurrence of muscular symptoms in the nuchal region, sometimes accompanied with headache, was noted after the ingestion of certain foods. The same symptoms could be reproduced experimentally by ingestion of the specific food, and their recurrence could be prevented by elimination of the offending food from the diet. This was also found to be true in cases of exposure to specific inhalants, such as house dust.

Five cases are described in which pulling, drawing, tautness, aching, stiffness and decreased mobility of the posterior cervical muscles were among the symptoms which followed ingestion of food allergens or exposure to specific inhalants. Headache was associated with the nuchal symptoms at times. Involvement of the neck muscles is the most frequent manifestation of allergy affecting the skeletal musculature, but other muscles or groups of muscles may be involved also. All symptoms of this type are not of allergic origin, but in the absence of a definite etiological agent the relationship of allergens to this syndrome should be considered.

RYAN, Philadelphia.

PALATAL MYOCLONUS. VICTOR R. ALFARO, Arch. Otolaryng. **51**:65 (Jan.) 1950.

Palatal myoclonus is a symptom complex consisting of clonic contractions of the tubo-palatal muscles and characterized by visible dimpling or elevation of the soft palate and a subjective or objective tinnitus, usually described as a clicking or ticking sound. The contractions are not rhythmical, vary in rate from 80 to 150 per minute and may be unilateral

or bilateral. Most authorities believe that the tinnitus is due to the sudden separation of the moist walls of the eustachian tube when the tubal muscles contract. This can easily be differentiated from vascular tinnitus, which has a soft, blowing murmur synchronous with the pulse. Studies of autopsy reports in cases of palatal myoclonus suggest that the pathological process is a degenerative lesion in the brain stem. Palatal myoclonus has developed in several cases after gun explosions, and in at least two other cases cures by hypnosis were reported. In view of the latter facts, a brain lesion fails to explain the pathologic process in all cases of palatal myoclonus.

RYAN, Philadelphia.

INFLUENCE OF THE AUTONOMIC NERVOUS SYSTEM ON THE CEREBRAL BLOOD SUPPLY. A. DE SAUSA PEREIRA, Arch. Surg. **60**:456 (March) 1950.

Disturbances of cerebral blood supply caused by arterial occlusion or spasm can be relieved or improved by bilateral cervical sympathectomy combined with periarterial sympathectomy of the carotid and vertebral arteries. In six cases of cerebral vascular lesions, such as thrombosis of the carotid artery or of its branches, or post-traumatic cerebral vasospasm, angiography was employed before and after sympathectomy to demonstrate the postoperative widening of the cerebral vascular bed. In all instances there was clinical improvement of the neurological and psychic changes.

LIST, Grand Rapids, Mich.

LEAD IN RELATION TO DISSEMINATED SCLEROSIS. A. M. G. CAMPBELL, G. HERDAN, W. F. T. TATLOW and E. G. WHITTLE, Brain **73**:52, 1950.

Campbell and associates investigated the relation of lead to disseminated sclerosis in several aspects. They located two areas in which disseminated sclerosis occurred with increased frequency among people living in close proximity to each other. In these areas there was an excessive amount of lead in the soil and/or water. They described two cases of lead myelopathy which may be considered cases of progressive disseminated sclerosis. Finally, they determined the lead content of the teeth of patients with disseminated sclerosis, spastic paraplegia and retrobulbar neuritis and found the amount of lead to be significantly greater in these patients than in normal persons. The authors believe that exposure to lead is one of the causes of excessive amounts of lead in teeth. They suggest that lead plays an etiological role in disseminated sclerosis. It may interfere with an essential mineral, vitamin or enzyme reaction and thus precipitate demyelination.

FRANKEL, Philadelphia.

PAGET'S DISEASE AND INTRACRANIAL TUMOR: ASSOCIATION OF AN ASTROCYTOMA OF RIGHT TEMPORAL LOBE WITH OSTEITIS DEFORMANS. M. N. ESTRIDGE, Bull. Los Angeles Neurol. Soc. **15**:87 (June) 1950.

Estridge reports the case of a man aged 32 with slowly enlarging head, left homonymous hemianopsia, diplopia and symptoms of increased intracranial pressure. Roentgenograms showed Paget's disease (osteitis deformans) of the skull. Ventriculograms suggested tumor of the temporal lobe. Exploration revealed a tumor, and partial removal of an astrocytoma of the right temporal lobe was performed. The patient survived 22 months, with reoperation and roentgen therapy.

In reviewing the literature, the author found no cases in which increased intracranial pressure or homonymous hemianopsia occurred in an uncomplicated case of osteitis deformans. In patients with increased intracranial pressure or signs suggestive of intracranial disease the existence of a brain tumor must be suspected.

ALPERS, Philadelphia.

TRAUMATIC PNEUMOCEPHALUS. E. T. YUHL, Bull. Los Angeles Neurol. Soc. **15**:93 (June) 1950.

Traumatic pneumocephalus may be subdivided into three main types, based on the anatomic location of the fracture of the skull, namely, frontal, temporal and occipital. By far the most frequent is fracture of the frontal area; less so, fracture of the temporal area, and rarest,

fracture of the occipital bone. These fractures may be produced by many forms of trauma. The air may lodge in the subdural space, in the subarachnoid space, within the ventricles or within the brain. Subdural collection of air is commonest and subarachnoid collection least so.

The diagnosis of pneumocephalus is relatively simple when the examiner considers the possibility of its presence, which, for the most part, depends on a history of cerebrospinal rhinorrhea. A controversy revolves about the question of operative intervention. Some authors state that recovery follows a conservative regimen of bed rest, supportive therapy and antibiotic and chemotherapeutic agents. Others feel that the ever present danger of a fatal infection necessitates immediate surgical intervention.

The case here reported is the occurrence in a white man aged 34 of a comminuted, depressed fracture of the left frontal bone with extension to the left orbit, followed by a brief episode of cerebrospinal rhinorrhea. Post-traumatic sequelae included severe generalized, persistent headache and periodic jacksonian and grand mal convulsions. Subsequent injury to the back of the head four years later caused the development of the characteristic symptom complex of pneumocephalus 10 days after injury. Surgical intervention was undertaken, with benign postoperative course and recovery.

This case has several interesting and unusual features. A four year latent period intervened between the time of the original injury to the skull and the onset of pneumocephalus. Stress must be placed on the significance of the air cyst. With repeated insult to the brain tissue as air is forced into the skull, there is progressive, irreversible damage. This patient showed complete destruction of the left frontal lobe and clinically presented many symptoms directly attributable to this damage.

With recent improvements in surgical technic and postoperative care and with the advent of antibiotics, the mortality rate in such cases is being reduced. In view of these facts, it is the opinion of the author that operative intervention is the only means of effectively preventing further cerebral damage.

ALPERS, Philadelphia.

AMNESIA FOR LEFT LIMBS AND LOSS OF INTEREST AND ATTENTION IN LEFT FIELDS OF VISION. K. E. FRANTZ, J. Nerv. & Ment. Dis. **112**:240 (Sept.) 1950.

Frantz reports a case of distortion of body imagery manifested by failure to recognize blindness and inattention on the left side of the body resulting from a lesion in the right parieto-occipital area. The patient, a man aged 55, had a large metastatic bronchogenic carcinoma in the right occipital lobe, extending into the parietal lobe, and a smaller tumor in the left occipital lobe. During life he lacked awareness of the left homonymous hemianopsia and seemed to pay no attention to his left limbs. Examination of the visual fields revealed the hemianopsia only when the two eyes were tested simultaneously. He had astereognosis of the left hand and manifested extinction of perception of stimuli on the left side when the two sides were stimulated simultaneously.

BERLIN, Chicago.

A SARCOID FORM OF ENCEPHALITIS IN A PATIENT WITH HODGKIN'S DISEASE. A. ROTTINO and G. HOFFMAN, J. Neuropath. & Exper. Neurol. **9**:103 (Jan.) 1950.

Rottino and Hoffman discuss a form of Hodgkin's disease of the central nervous system which bears a resemblance to viral encephalitis and report a case of concurrent encephalitis and Hodgkin's disease in a man aged 37.

The authors again raise the question of whether Hodgkin's disease of the brain exists. The picture of Hodgkin's disease in the lymph nodes was typical in this case; the lesions in the central nervous system were not. Nowhere was necrosis observed, nor were the Sternberg-Reed cells seen.

In order to find evidence for or against the theory of the relation of encephalitis to Hodgkin's disease, the authors reviewed 80 cases of incontrovertible Hodgkin's disease and the autopsy material from 40 cases. They found two cases in which lesions of the central nervous system similar to those in the present case were observed.

ALPERS, Philadelphia.

CLINICAL STUDY OF PRIMARY SYPHILITIC OPTIC ATROPHY. C. LAMOTTE DE GRIGNON NICOLAU, Encéphale **38**:477, 1949.

This article is based on a close review of the literature and a careful study of 43 cases collected from the observations of Guillain and Alajouanine at the neurologic clinic of the Salpêtrière. The author notes that among the clinical forms of tabes the amaurotic type is characterized by mild or no spinal signs associated with a more or less pronounced deficiency in visual acuity. There appears to be a certain incompatibility between the blindness and the ataxia.

Nevertheless, the author reports a case of what he calls "ataxic and amaurotic tabes with acute development, not modified by either early medical or surgical treatment." This was the case of a man aged 39, a journalist, who began to have visual trouble in May 1948. In June tabetic lightning pains appeared, and in August the diagnosis was made. Again, in October, examination revealed bilateral syphilitic primary optic nerve atrophy. In November 1948 he was bedridden by his spinal disabilities, with the complete picture of tabes. Ten bouts of malarial fever and 15,000,000 units of penicillin gave no relief. Operation revealed optochiasmatic arachnoiditis. Such a case is rare in the literature.

The author concludes from the study of the series of 33 cases that the amaurotic type of tabes is a well delimited clinical variety of the common form of the disease. This form nearly always begins with the difficulties in vision; spinal symptoms are usually less frequent and less intense. The lesions of the optic nerve reveal two types of development. In the first type there is a benign optic nerve atrophy, which begins insidiously, has a slow course and only exceptionally ends in blindness. In this type the spinal symptoms of tabes are not so rare as in the second type. Also, in the first type vision is often improved by therapy, and the prognosis is not so grave. This type is seen not only with tabes but also with dementia paralytica and with syphilitic myelitis, as well as with other forms. The optic nerve atrophy is rarely of the malignant type.

In the second type, seen only with tabes, the optic nerve atrophy is malignant; onset is sudden, and the process develops rapidly, ending in blindness in less than one year in most cases. In this type the spinal tabetic symptoms are exceptional or very mild. Treatment is less helpful, and the prognosis is grave.

The author notes the following characteristic clinical symptoms of tabes associated with primary optic nerve atrophy: 1. The onset is with a decrease in visual acuity in a majority of the cases. 2. Spinal symptoms are less pronounced and less frequent than in the common form of tabes. Paresis or paralysis of the third nerve is present with the same frequency as in the common form of tabes. 3. In the 33 cases of tabes with primary optic nerve atrophy which he studied, there was no instance of mental disturbance. 4. The visual diminution does not follow the same course in all patients; in the group of tabetic patients with primary optic nerve atrophy who were not treated (acting as controls), some became blind rapidly, whereas others, a majority, retained fair vision. 5. There appeared to be no relation between visual trouble and incoordination. The two types seem to have an independent development. 6. A well conducted therapeutic attack seems to reduce the rapidity of progression of the atrophy. Some authorities believe that it even arrests the process. Nevertheless, even the most favorable statistics reveal a percentage of cases in which blindness could not be avoided.

The pathogenesis is not the same in any 2 cases. In the malignant form, toxic and allergic factors, either together or alone, seem to be responsible for the rapidity and irreversibility of the parenchymal lesions of the nerve. On the contrary, in the benign form, characteristic of dementia paralytica, the lesions are related to the inflammatory process in the nerve sheath and the lesions of the optic nerve are merely secondary. A third, mechanical, factor may be added in certain cases. This is the direct or indirect action of the optochiasmatic arachnoiditis; it is rarely the principal cause of the atrophy. The results of therapy will differ in the two forms.

The preferred treatment is a combined form—administration of penicillin, malaria therapy and chemotherapy. Surgical treatment is indicated when there is evidence of intracranial hypertension. Prophylaxis means a constant watch over every syphilitic person, particularly those showing no neurologic signs, for diminution of vision is often the first sign in a majority of these patients.

ZINKIN, New York.

THE SYNDROME OF PUBERTAS PRECOX, ADIPOSITY, POLYDACTYLY, OLIGOPHRENIA AND EPILEPSY ASSOCIATED WITH A LOCALIZED MALFORMATION IN THE HYPOTHALAMUS. B. BROUWER and R. BRUMMELKAMP, Folia psychiat. neurol. et neurochir. **51**:184 (Aug.) 1948.

Brouwer and Brummelkamp report the case of a man aged 20 with epilepsy, pubertas precox, mental deficiency, obesity and polydactyly. Autopsy revealed a sharply circumscribed disturbance of development in the ventral portion of the hypothalamus. The tuber cinereum was hyperplastic, owing to increase of neuroglia and the intermediate tissue, and embryonic cells were observed in the same area. The number of normal ganglion cells in this region was greatly decreased, and there was an inhibition of development of various nuclear groups of the tuber cinereum. The medioventral hypothalamic nucleus could not be identified as such, and the mamillary bodies participated in the failure of development. They were small, deformed and poor in cells. The cells of the perifornical nuclei were decreased in number, and the mamillothalamic bundle was poorly developed bilaterally.

The syndrome differed from the Laurence-Moon-Biedl syndrome in the absence of retinitis pigmentosa. The case is important because of the distinctly localized lesion which appears to have been responsible for the syndrome.

ALPERS, Philadelphia.

CHRONIC SUBDURAL HAEMATOMA. A. VAN DER ZWAIN, Folia psychiat., neurol. et neurochir. **51**:385 (Dec.) 1948.

Van der Zwan reports 43 cases of subacute or chronic subdural hematoma. Of these, a severe head injury had been sustained from two weeks to four months previously in 10, and a trivial head injury, from two to twenty-one months before in 16; in 17 no trauma could be demonstrated. Most of the patients were between 50 and 80 years of age. Van der Zwan found that the headache, at first mild, became severe and paroxysmal in 50 per cent of the cases during the latter part of the illness. Papilledema was found in 10 cases; impairment of ocular movements, in 27 cases; disturbance in pupillary reactions, in 12 cases; contralateral hemiparesis, in 8 cases; ipsilateral hemiparesis, in 5 cases, and generalized seizures, in 6 cases.

ALPERS, Philadelphia.

Diseases of the Spinal Cord

MOTOR MANIFESTATIONS OF HERPES ZOSTER: REPORT OF A CASE OF ASSOCIATED PERMANENT PARALYSIS OF THE PHRENIC NERVE. S. L. HALPERN and A. H. COVNER, Arch. Int. Med. **84**:907 (Dec.) 1949.

Halpern and Covner report a case of permanent paralysis of the phrenic nerve with herpes zoster, since it is unparalleled in the literature.

In a white man aged 53, ten days after acting as a blood donor, the right arm having been used, there developed an excruciatingly painful vesicular eruption. This blossomed out as typical herpes zoster involving the third and fourth cervical segments on the right side. Three days after the eruption reached its maximum, shortness of breath developed. This was not associated with cough or pain in

the chest. Physical examination was noncontributory. Under symptomatic treatment the eruption began to dry up in ten to fourteen days, and it eventually cleared, except for residual scars and exertional dyspnea. When seen one year later, the patient complained only of dyspnea, especially on exertion but also after meals and on bending over. A diagnosis of paralysis of the right side of the diaphragm was made. Complete examination at that time and almost eleven months later revealed the same physical signs, namely, scars in the region of the third and fourth cervical dermatomes on the right side, slight elevation of the right side of the diaphragm, which failed to descend on deep inspiration, and a positive Hoover sign. Fluoroscopic examination revealed paralysis of the diaphragm on the right side.

The diagnosis was therefore made of exertional dyspnea due to paralysis of the phrenic nerve associated with zoster. This diagnosis was justified by the concomitant onset of the two processes, the association of spinal segments in the two conditions and the failure to find any other cause for paralysis of the phrenic nerve and the diaphragm or for symptomatic dyspnea. There was no improvement in the patient's condition during the time of observation. Since the paralysis was of almost two years' duration, it was felt that it could be classified in the permanent category. Whether the infection was introduced during the venipuncture when the patient served as a blood donor could not be judged.

Motor manifestations are an integral part of the neurodermatologic disorder of herpes zoster and are a result of the basic pathologic process. The authors point out that motor symptoms, especially those of a mild and transitory nature, occur frequently and urge that they be specifically looked for. Destruction of motor neurons in the anterior horns or of the nuclei of origin of the motor cranial nerves may result in permanent paralysis.

ALPERS, Philadelphia.

SPINAL SUBDURAL ABSCESS DUE TO A CONGENITAL SINUS AND ACCOMPANYING CHANGES IN THE AUTONOMIC NERVOUS SYSTEM. ARTHUR B. KING and CURT P. RICHTER, Bull. Johns Hopkins Hosp. **85**:431 (Dec.) 1949.

King and Richter report the case of a patient who was born with an intradural dermal sinus in the lower lumbar and sacral parts of the spinal canal. It drained freely through an opening between the fourth and the fifth lumbar vertebra. At the age of 4 months the sinus became infected, and at the age of 7 months the excision of the extradural part occluded the sinus and blocked the drainage from the intradural portion. The resulting increase of pressure must first have caused the sinus to become very distended, and later may have caused it to rupture, allowing the enclosed pus to spread freely through the subdural space. Pressure from the abscess and/or local inflammatory action on the spinal roots produced widespread asymmetric changes in the motor, sensory and autonomic nervous system. Below the eleventh and twelfth thoracic dermatomes the effects were bilateral; above, strictly unilateral.

At the end of the first year drainage of the sinus and treatment with penicillin brought almost immediate relief. The child quickly became able to walk and to carry on many activities. Two years later, when all the infection had subsided, the intradural part of the sinus was readily removed, but some of the sacral roots may have been injured in the process. The child made a rapid recovery. Sympathetic, motor and sensory changes were still present, however, mainly on the right side, in the now 5 year old child.

Examinations of electrical skin resistance showed that the effects produced by the subdural abscess on the sympathetic nervous system were strictly unilateral. No deviation from normal levels of resistance were observed at any time on the left side of the body, in spite of the presence on that side of definite alteration in sensory and motor functions. The effects produced on the sympathetic nervous

system were, in this case, long lasting, being present even after five years, though in greatly diminished intensity. They persisted longest in the head and upper thoracic region, the parts of the body farthest removed from the site of the sinus. It is noteworthy that these changes were present in the absence of any abnormalities of the sensory and motor system in this part of the body. The plantar surface of the right foot showed an area with an apparently permanent sympathetic denervation.

ALPERS, Philadelphia.

Peripheral and Cranial Nerves

THICKENING OF SUPERFICIAL NERVES AS DIAGNOSTIC SIGN IN LEPROSY. J. R. MURDOCK, Internat. J. Leprosy **17**:1, 1949.

That the superficial nerves are commonly involved in leprosy impressed Murdock during three years of intensive study of the disease at the Kalihi Hospital, Honolulu, Territory of Hawaii. The author presents results obtained in an intensive study of the nerves of 117 ambulatory patients. Notes on 5 cases are given to show the involvement of superficial nerves in the early stages of the disease. They demonstrate that during cutaneous exacerbations the superficial nerves are commonly involved. Repeated intensive examinations of the children of leprous parents indicated that the superficial nerves may be involved and demonstrable before other characteristic signs are present. The author feels that the finding of definitely thickened superficial nerves in a case of suspected leprosy is one of the most important signs in a differential diagnosis of leprosy. In bacteriologically negative cases the finding of thickened superficial nerves in conjunction with anesthetic areas and cutaneous lesions clinches the diagnosis of leprosy.

J. A. M. A.

LATE PARALYSIS OF THE ULNAR NERVE FOLLOWING FRACTURE OF THE ELBOW. E. BERGMANN, Monatsschr. f. Psychiat. u. Neurol. **117**:203 (April) 1949.

Bergmann states that late paralysis of the ulnar nerve is a sequel of fracture of the lateral condyle of the humerus in childhood. About twenty years elapse before neuritic manifestations appear, and then sensory changes precede the motor. This condition has a basis in the fact that a fracture of the external condyle of the humerus does not show osseous healing but remains in a loose connective tissue union with the humerus. As the distal end of the humerus, particularly the medial portion, grows, the forearm is displaced in a cubitus valgus position. The younger the child at the time of the fracture, the greater the deformity at the cessation of growth. Because of the angulation in the elbow joint, the ulnar nerve has to take a circuitous course and is placed under considerable tension. Apparently, this is a slow process, and many years intervene before definite symptoms arise. Basically, this condition occurs because of the inadequate treatment of the fracture, which necessitates operative methods, with a nail, screw or bolt used to effect union of the fragments.

To relieve the mechanical basis of the disorder, the tension on the nerve must be diminished. This can be achieved by operation. An osteotomy of the distal end of the humerus can correct the cubitus valgus; but, since the deformity of the elbow joint itself is not incapacitating, it is much easier to perform a neurolysis and raise the ulnar nerve from its course behind the elbow, replacing it along the flexor surface. This operation effects a shortening of the pathway of the nerve. The transposition of the nerve must be undertaken as soon as the condition has been recognized, because if the repair is neglected until motor manifestations appear the prognosis even after operation becomes less favorable.

PISETSKY, New York.

Muscular System

HEREDITARY FACTORS IN INFANTILE PROGRESSIVE MUSCULAR ATROPHY: STUDY OF 112 CASES IN 70 FAMILIES. SWEN BRANDT, Am. J. Dis. Child. **48**:226 (Aug.) 1949.

Genetic studies were made on 70 families with 112 cases of infantile hereditary progressive spinal muscular atrophy (Hoffmann-Weidnig syndrome) among siblings and a few similar cases among more distant relatives. Recessive inheritance, causing the disease to appear in homozygous children born of two conductors, was the probable cause in most cases. A consanguinity rate of 5.8 per cent (eight times higher than that for a control group) justified this conclusion. Other observations suggested that more complicated genetic factors were present in some cases.

JOHNS, Philadelphia.

PROGRESSIVE MUSCULAR DYSTROPHY INVOLVING THE EXTRAOCULAR MUSCLES. SAMUEL GARTNER and EDWIN BILLET, Arch. Ophth. **41**:334 (March) 1949.

In the opening paragraph of their paper, the authors present their problem. "The diagnosis of palsy of an extraocular muscle usually signifies to the ophthalmologist a lesion of its nerve supply. For example, a paralysis of the external rectus muscle is accepted as indicating a lesion of the sixth nerve or of its nucleus. This is so common that there is a great tendency to forget the rarer occurrence of a primary muscular disorder as a cause of impairment. Many such errors appear in the literature; a critical review of the published reports since 1890 indicated that in some of the cases of ophthalmoplegia the paralysis was due not to the nerve lesions to which it was ascribed, but probably to myasthenia gravis or to one of the types of muscular dystrophy."

Gartner and Billet report the case of a white man aged 26 with a profound degree of emaciation and wasting of all muscle groups. Examination of the ocular muscles showed generalized paresis of all the extraocular muscles, of varying amount, most pronounced in the internal rectus muscles. A resection of the left internal rectus muscle was performed for improvement of the squint. At that time some of the internal rectus muscle was obtained for histologic study. Two pieces of muscle tissue were removed, one near the tendinous insertion of the muscle on the globe and another farther back, in the belly of the muscle.

Histologic examination of the excised muscle showed extensive changes. "Most of the myofibrils were swollen and degenerated, with some replacement by fibrous tissue and loss of their cross striations. There was an increase in the number of sacrolemmal nuclei. A small number of myofibrils had some resemblance to the normal, but even these took the stain poorly; their outlines were a bit irregular, and their cross striations were faint. A few myofibrils were vacuolated, as in lipid degeneration. This confirmed the diagnosis of muscular dystrophy. . . ."

"Progressive muscular dystrophy was the cause of ptosis and divergent squint in the case presented. . . . This case is the second in which histologic study of the extraocular muscles has been reported and the first in which involvement of the extraocular muscles has been demonstrated in a case of generalized progressive muscular dystrophy."

SPAETH, Philadelphia.

Experimental Pathology

CHROMATOLYTIC EFFECT OF CEREBROSPINAL FLUID FOLLOWING CEREBRAL CONCUSSION. E. A. SPIEGEL, M. SPIEGEL-ADOLF and H. T. WYCIS, Science **105**:208 (Feb. 21) 1947.

After cerebral concussion, the cerebrospinal fluid is able to split nucleic acids, as shown spectrophotometrically by a decrease in their selective absorption in ultraviolet light. This finding was interpreted to be due to the appearance of enzymatic substances in the cerebrospinal fluid. It seemed of interest to ascertain whether

such substances diffusing into the subarachnoid space after concussion are also able to act on nuclear substances within nerve cells, in particular, the tigroid bodies.

A method is described for obtaining suitable preparations for the demonstration of Nissl bodies. The incubation of sections in acidified normal cerebrospinal fluid or in Ringer's solution was found to leave intact most Nissl bodies of the motor cells in the spinal cord of the cat, whereas some cerebrospinal fluid of patients with concussion produced definite tigrolysis in the anterior horn cells under identical conditions. Spectrophotometric studies corroborated these findings. Thus, the histochemical and the spectrographic method confirmed each other.

The demonstration in the cerebrospinal fluid of patients with concussion of substances able to produce dissolution or a breakdown of Nissl bodies seems of interest for various reasons. From a clinical, as well as a medicolegal, point of view, the demonstration of changes in the cerebrospinal fluid following cerebral concussion may be of value, particularly when other objective signs of damage of nerve cells are scarce or lacking. These findings may also shed light on the pathologic changes developing in the brain after a blow to the head. If enzymatic substances diffuse from the central nervous system into the cerebrospinal fluid, it seems reasonable to suspect that such substances play an important role in the genesis of the chromatolytic changes occurring in vivo after concussion.

GUTTMAN, Philadelphia.

Congenital Anomalies

INHERITANCE OF ARACHNODACTYLY, ECTOPIA LENTIS AND OTHER CONGENITAL ANOMALIES (MARFAN'S SYNDROME) IN THE E. FAMILY. FRANK C. LUTMAN and JAMES V. NEEL, Arch. Ophth. **41**:276 (March) 1949.

The authors report in detail an exhaustive consideration of the syndrome under discussion. In a kinship of 40 persons, 17 members probably had the syndrome. There was a great variability in its expression in the affected members. In addition to classic cases, there existed in the family cases so mild that the diagnosis would have been unsuspected or in doubt had it not been for the genetic background.

Ocular anomalies observed in all persons studied, in addition to either ectopia lentis or coloboma of the lens, were abnormal zonular fibers, an iris lacking in the usual surface trabeculae and crypts, deficiencies of uveal pigment, particularly at the periphery of the iris, and amblyopia. In several cases these were accompanied with other ocular defects.

The syndrome is inherited as though due to one or more dominant autosomal genes. Although a final decision is not possible, the bulk of the evidence suggests that the entire syndrome may be due to one gene only, the expression of which is greatly influenced by other genetic, and possibly by environmental, factors.

"The disease is undoubtedly much commoner than the 200 or more described cases would indicate. From the broadly biologic standpoint, it is one of the most interesting diseases known to ophthalmologists. If the frequency of the syndrome could be established, an approximate estimate of the mutation rate would be feasible; from what little is now known, it appears that this mutation rate would be 'high' by the standards used in judging mutation rates for Drosophilia and corn. The detailed description of further extensive pedigrees is highly desirable. It is possible that the mutation process gives rise to a number of distinct alleles and that the relative mildness of the disease in this kinship is due to the occurrence of an allele with less pronounced effects than usual.

"In view of the threat to survival and reproduction imposed by Marfan's disease, it is felt that the syndrome would quickly disappear through natural selection unless there were a relatively high mutation rate from normal to the gene responsible for this syndrome. The many isolated cases which have been reported are thought for the most part to represent the results of this mutation process."

SPAETH, Philadelphia.

Society Transactions

CHICAGO NEUROLOGICAL SOCIETY

Alex J. Arieff, M.D., *President in the Chair*
Regular Meeting, March 14, 1950

Pattern of Localization in the Precentral Motor Cortex of Macaca Mulatta. Dr. C. N. Woolsey and Dr. P. H. Settlage, Madison Wis.

Somatic sensory and motor areas of the rat's cerebral cortex are so organized as to form somewhat distorted body images in which the various parts are related to one another much as in the actual animal. The sensory and the motor patterns are mirror images, touching one another at the snout and limb apex along a line which corresponds to the central sulcus of primates (Woolsey, C. N., and others: *Federation Proc.* **7**:137, 1948; **8**:144, 1949).

On reexamination of the localization pattern in the precentral gyrus of the monkey, we have been surprised to find that the motor pattern of this animal hangs together as it does in the rat and that the accepted separation of face from trunk is not a fact. In essence, the fingers, toes and lower part of the face are represented within and adjacent to the central sulcus. The axes for the arm and leg run rostrocaudally, so that proximal parts of the limbs are better represented rostrally, as are the upper part of the face, the eyelids and the pinna. Binding together the face, arm and leg representations is an area for axial musculature, which forms the rostral border of the pattern. This border corresponds approximately to the rostral limit of 4 s, or the boundary between area 6 a α and area 6 a β of Vogt, as judged from gross brain maps. The abdominal musculature is represented between arm and leg areas nearer the central sulcus. The results raise the question whether the usual separation of the precentral region into physiologically distinct motor and premotor fields is justifiable.

Interconnections Between the Anterior Lobe and the Paramedian Lobule of the Cerebellum. Dr. J. W. Barnard and Dr. C. N. Woolsey, Madison, Wis.

The projections of the tactile areas of the body to the anterior lobe and the paramedian lobule of the cerebellum suggest that these two areas may be functionally related to one another. Somatic area I of the cerebral cortex optimally excites the anterior lobe, and somatic area II is related to the paramedian lobule in the same way; finally, since somatic area I and somatic area II are closely interrelated, it would appear that the anterior lobe and the paramedian lobule might be similarly connected.

Stimulation of the lobulus centralis of the anterior lobe of the cat gives good responses in the leg area of the paramedian lobule of the same side. The culmen projects to the middle, or arm area, folia of the paramedian lobule. Electrical stimulation of the arm and leg areas of the paramedian lobule gives responses in the ipsilateral portion of the culmen and lobulus centralis, respectively. That antidromic conduction is not responsible here is evinced by the latencies of close to 6 milliseconds, which are long enough to lead to the conclusion that one or more synapses are present. Decerebration does not interfere with the responses, indicating that levels above the midbrain are not involved. Complete cutting of all cerebellar peduncles does not abolish the responses, indicating that they are intracerebellar.

Effect of Intravenous Injections of Urea on Cerebrospinal Fluid Pressure in Monkeys. Dr. Paul H. Settlage, Madison, Wis.

Six monkeys were used to compare the effects of intravenous injection of dextrose, sucrose and urea on cerebrospinal fluid pressure. Each animal was subjected to five injections on as many experimental days. The five doses were as follows: 5 cc. of 50 per cent dextrose, 5 cc. of 50 per cent sucrose, 5 cc. of 1.7 per cent urea, 1.7 cc. of 50 per cent urea and 5 cc. of 50 per cent urea, per kilogram of body weight.

The dextrose produced an average fall in pressure of 41 mm. of Ringer's solution, and the 5 cc. per kilogram of 50 per cent urea, an average fall of 188 mm. The duration of the decreased pressure was 50 minutes in the case of dextrose. The pressure at the end of the period of observation (four to six hours) following injection of 5 cc. per kilogram of 50 per cent urea was in all cases lower than the maximum decrease following dextrose. The other substances produced effects which were intermediate in degree.

No toxic effects were noted other than a transient hemoglobinuria following the use of 50 per cent urea solutions. The hemoglobinuria was assumed to be due to hemolysis occurring at the time of injection.

DISCUSSION

DR. W. A. GUSTAFSON: During the war we gave urea orally in all the cases of meningitis which were intractable with sulfadiazine. We also gave urea with sulfadiazine in these cases. I wonder whether one would get the same results with the oral use of urea as with the intravenous use. We did not have the facilities to sterilize properly for intravenous injections, but the blood findings were the same with the oral as with the intravenous administration of urea.

DR. PAUL SETTLAGE, Madison, Wis.: One would expect to obtain a decrease with the oral use of urea, though possibly not as great as by the intravenous infusion. We have been unable to test this effect in the animals, since peristalsis is not adequate with the animal under anesthesia.

DR. R. P. MACKAY: Since urea is a powerful diuretic, I should like to ask whether diuresis was noted in these animals and whether dehydration was observed in the rest of the body.

DR. PAUL H. SETTLAGE, Madison, Wis.: Diuresis was not checked systemically, though there is no doubt that it was profuse. I have used urea in experimental neurosurgery, and there is a visible shrinkage of the tissues of the central nervous system, due no doubt to dehydration.

DR. JOHN MARTIN: Have the authors made any histological studies on the kidneys and brain, and did they see any damage in these structures? What was the rate of the return of pressure to normal after the injections?

DR. PAUL H. SETTLAGE, Madison, Wis.: We made no histological studies. With 5 cc. of 50 per cent urea per kilogram, the pressures never returned to normal during the experimental period, which was more than six hours in some cases.

DR. ALEX J. ARIEFF: Was the cerebrospinal pressure reduced or decreased from the normal state or from an increased reduced state? If from an increased state, how was this induced?

DR. PAUL H. SETTLAGE, Madison, Wis.: The pressures were all reduced from the normal state.

Effects of Picrotoxin and Sodium Succinate on the Electroencephalographic Changes Accompanying Amobarbital Hypnosis. DR. MARC J. MUSSER JR., DR. WARREN E. GILSON and HULDA R. GIESCHEN, Madison, Wis.

Twenty-four healthy adults whose electroencephalograms were normal were given a 6.5 per cent solution of amobarbital sodium (sodium amytal®) intravenously (715 mg. to 1.0 Gm. of amobarbital sodium) until a level of hypnosis manifested by unconsciousness, constricted and fixed pupils, corneal anesthesia and shallow respiration was obtained. There was then given an 0.1 per cent solution of sodium succinate or a solution containing 12 per cent sodium succinate and 12 per cent dextrose intravenously until consciousness returned. To accomplish this effect, 12 to 20 mg. of picrotoxin and 5.5 to 20.0 Gm. of sodium succinate were necessary. Seven subjects receiving amobarbital sodium alone served as controls. Continuous six channel electroencephalographic recordings, with conventional electrode placement, were made throughout each experiment.

The electroencephalographic changes accompanying the administration of amobarbital sodium consisted of an increasing amount of high voltage (50 to 200 microvolts), fast activity (15 to 20 per second) and, as hypnosis deepened, occasional equally high voltage, 3 to 4 and 4 to 6 per second, notched, flat-topped waves.

Neither pictrotoxin nor sodium succinate influenced the electroencephalographic changes resulting from amobarbital sodium. From this it may be deduced that neither drug significantly modified the metabolic effects of amobarbital sodium on the brain.

The rate of recovery from the amobarbital hypnosis was accelerated by picrotoxin. It was not influenced by sodium succinate.

Clinical Observations on Patients with Glioblastoma Multiforme Who Have Received Radioactive Phosphorus. Dr. T. C. Erickson and Dr. H. F. Steelman, Madison, Wis.

Previous studies have indicated that radioactive phosphorus is taken up by glioblastoma multiforme and other brain tumors in a greater concentration than it is by the surrounding cerebral tissue. Chemical fractionation has shown that the highest concentration is early in the acid-soluble fractions but, with accumulation of the P^{32}, later in the nucleoproteins (Erickson, T. C.; Larson, F., and Gordon, E. S.: *J. Lab. & Clin. Med.* **34**:587, 1949). An inhibitory effect on the tumor growth might be expected if an effective concentration of the radioactive material could be maintained, particularly if it could be maintained in the nucleoproteins. While recognizing that limiting factors, such as the high rate of uptake of the P^{32} by other tissues, might prove an obstacle in obtaining a therapeutic effect, it seemed that study of this problem in a group of patients with glioblastoma was indicated.

Twenty-six patients with histologically verified glioblastoma multiforme were given radioactive phosphorus (P^{32}). All but four patients had a generous removal of tumor; two of the 24 had only a bony decompression. The radioactive material (given as phosphoric acid) was administered in the immediate postoperative period, and to some patients a second dose was given later. To most patients it was given by mouth or intravenously, but in two patients it was injected into the carotid artery, and in two, directly into the tumor bed. Patients who died in the immediate postoperative period were excluded from the statistics The percentage of patients surviving was plotted against the months following operation. Values for control series of patients with the same type of tumor from this clinic, as well as other clinics, were plotted on the same chart, for comparison.

The dose of P^{32} varied from 2 to 25 millicuries, and in most patients the appearance of a mild temporary leukopenia was taken as an end point. Autopsy of the bone marrow has shown no permanent damage to the hemopoietic elements. A patient who died 12 hours after injection of 10 millicuries directly into the tumor had acute hepatic necrosis, but other factors may well have been responsible.

In seven patients the brain was examined post mortem. In two others biopsy specimens were examined several months after administration of P^{32}. No microscopic changes specifically attributable to radioactivity were found.

The average survival was 6.4 months. The survival curve for patients who received P^{32} does not indicate that their life expectancy was increased. The survival period for a control series of patients who had surgical removal but no radiation therapy averaged 8.6 months, and that for the series treated surgically and with high voltage radiation averaged seven months.

In conclusion, these results indicate that radioactive phosphorus administered in the manner described to patients with glioblastoma multiforme has no demonstrable effect on the growth of the tumor. Even though the relative concentration is greater in the tumor than in normal brain, the local radioactivity is apparently not sufficiently great to inhibit the growth of or to destroy the neoplastic cells.

Alex J. Arieff, M.D., *President in the Chair*
Regular Meeting, April 11, 1950

Neurology and the Nervous System of Man: Presidential Address. Dr. Alex J. Arieff.

The knowledge of the structure and function of the nervous system of man has been derived chiefly from the study of man.

Since it is impossible to perform ablations of parts of the nervous system in man, many discoveries related to the function of the nervous system have been derived from such experiments as nature provides in disease and injury. Otherwise, approximations and analogies have been made from studies on animals, particularly primates. Nevertheless, much has been learned from clinical observations, coupled with pathologic studies.

The neurologist has been singularly prominent in such studies. [The numerous contributions of clinical men and neurologists to knowledge of the spinal cord, cerebral function, neurosurgery, cytoarchitecture, neuron theory, vegetative nervous system and the cerebellum were discussed.]

As one reviews, even sketchily, the contributors and contributions to knowledge of the nervous system of man, excluding nosological entities, one is struck with the basic grounding of the contributors, who were in great part clinicians. With their contributions as a foundation, one now has electronic aids, such as electromyography, electroencephalography and accurate measuring and amplifying aids; arteriography, pneumography and ventriculography, and a host of drugs, including the antibiotics and radioisotopes.

Use of Psychological Tests in Neurologic Diagnoses. Dr. Roy Brener.

A survey was made of the various areas in the field of neurology in which psychological tests and technics have been used. The growth in the use of psychological tests was traced historically up to the present time. Emphasis was placed on the role of clinical psychology in research, as well as in the development of new technics and the improvement of old ones for diagnostic purposes. In evaluating the psychological tools, consideration was given to their use in studying both the direct and the indirect psychological effects on the patient of his illness. Attention was given to a consideration of the direction that the future development of psychology in relation to neurology might be expected to take.

DISCUSSION

Dr. Roy Brener: Mr. Hutchins once asked one of the country's eminent clinical psychologists for a definition of clinical psychology and could not get a satisfactory response. In that case, I am sure I shall be forgiven if I do not do much better. This particular point, however, emphasizes the problem on which I wanted to focus attention. The role of the clinical psychologist is not clearcut in many cases because the discipline is a new and rapidly growing one. The number of psychologists in the American Psychological Association has increased severalfold in the last ten years. As clinical psychologists, our immediate problem, and perhaps one for several years to come, is that of clarifying our role in relation to other disciplines. It is definitely our problem; but so far as we work with other disciplines and have something to contribute to other disciplines, it becomes their problem, too, to help in clarifying the relationship and aid in determining the areas of collaboration. In the meantime, what the clinical psychologist does and is, is pretty much a function of the institution and the group with which he works. To clarify that role becomes the task not only of the professional groups but of the individual psychologists and the individual members of the other disciplines with whom the psychologist works.

Physical Medicine and Rehabilitation for Patients with Spinal Cord Injuries. Dr. Louis B. Newman, Hines, Ill.

A close integration of those concerned with the medical care and rehabilitation of patients with spinal cord injuries is essential. Though the total number of patients with this disability is relatively small in comparison with those having rheumatic diseases, heart disease, cancer, etc., the rehabilitation of these patients taxes one's ingenuity to the utmost. The goal of total rehabilitation is gainful employment. A readjustment and reorganization of the person toward his disability, physically, mentally, socially, psychologically and vocationally, is necessary.

The Physical Medicine Rehabilitation Service in the Veterans Administration consists of physical, occupational, corrective, educational, and manual arts therapies, under the direction of a physiatrist (physician specializing in physical medicine and rehabilitation). To integrate further the activities of all services and to plan the patient's hospital and posthospital program, a rehabilitation board has been established.

Through the use of heat, electrical stimulation, muscle reeducation and exercises, contractures are prevented or corrected, weakened muscles are strengthened, coordination is improved and function is increased. Braces, crutches and other assistive devices are used to accomplish self care and daily living activities, including ambulation. While hospitalized, patients receive treatment through occupational and manual arts therapy in such fields as radio, television, plastics, carpentry, leather technics, ceramics, photography and watch repair. Through educational therapy, elementary school certificates, high school diplomas and college courses can be secured.

Success in total rehabilitation depends on a careful evaluation of the patient's disability and prompt institution of rehabilitation procedures. Paraplegic patients are taught to drive hand-controlled cars with safety.

Physical medicine and rehabilitation will aid in securing for those with spinal cord injuries a place of usefulness, self respect and dignity.

DISCUSSION

DR. LEWIS POLLOCK: Although it may seem to an observer that the efforts of the department of physical medicine are devoted to teaching the patient to get about (imperfectly), to change his position from one place to another or to learn to care for himself, what actually is accomplished is to bring about a state of physical well-being, which, when compared with the situation which existed prior to this physical therapy, is almost unbelievable. One has only to recall the failure of bedsores to heal, the great numbers of calculi in the genitourinary system, the infections and the marked nutritional changes which occurred, to say that all who are the physicians of these patients owe this service a great debt. It is not difficult to sense the enormous patience one must have, as well as the ingenuity and the zeal to help these poor wounded veterans.

Alex J. Arieff, M.D., *President, in the Chair*
Regular Meeting, May 20, 1950

Visual Hallucinations Due to Irritation of the Occipital Lobe: Report of a Case.
DR. A. A. LIEBERMAN, Elgin, Ill.

An unusual opportunity was afforded by the case study of a white man aged 42 who suffered from congestive heart failure due to hypertensive vascular disease and generalized arteriosclerosis and who over the course of two years had recurrent, acute decompensation, responding rapidly to digitalization within some hours to several days. Concomitant with the onset of an acute period of generalized vascular decompensation were cerebral manifestations characterized by delusions of body scheme and, of greater interest, visual hallucinatory experiences of the variety observed as a consequence of irritation of the various visual centers of the occipital lobe, known anatomically as areas 17, 18 and 19. The visual hallucinations, characteristic of area 17, were of the primitive perceptive form of zigzag streaks of light. Those of area 18 were of a more elaborate nature, and those of area 19 were concerned with the higher integrative visual centers concerned in the process of revisualization of animate and inanimate objects. Closely correlated with the psychical manifestations were the postmortem findings, defined grossly by Dr. Arthur Weil, who, without foreknowledge of the case, was asked to determine the approximate duration of the lesions of the four areas of softening found in the occipital lobes. The correlations achieved were exceedingly high and supported the thesis that the hallucinatory experiences described by the patient were, at the time, due to cerebral irritative disturbances as a consequence of violent alteration in cerebral hydrodynamics, brought on by the generalized state of congestive heart failure.

The various theories of cerebral localization were considered. The role of spasm of the cerebral arterioles as the responsible agent in the production of irritative phenomenon was discussed. The theory of the role of spasm of the smallest vessels in the cortical mantle as a precursor to later softening was developed. Transient psychical symptoms, and, more especially,

fleeting hallucinosis, may be regarded as due to cerebral irritation. If this physiological alteration is sufficiently persistent, irreversible organic softening of the areas involved eventually ensues, as was found in the present case.

DISCUSSION

DR. FREDERICK HILLER: I wish to congratulate the speaker on the excellent presentation of what I would call a treasure of a case from a neurological, as well as from a psychiatric, standpoint.

I am not quite satisfied with the pathological diagnosis given in this case. Since the microscopic slides are here, there is no better opportunity to convince myself of the correctness of the diagnosis than by looking at them. I cannot agree with Dr. Lieberman's assumption that vascular stasis and vascular spasm were responsible for the localized softening and hemorrhage in the occipital area. I have had considerable experience, over many years, in studying cases of a similar kind, and I have come to the conclusion that apparent functional disturbances of the cerebral circulation, which in the end lead to organic lesions of the brain, are invariably associated with disturbances of the general circulation of the type seen, for instance, in acute heart failure. The history of this patient offers, I am sure, many indications pointing to the association of heart failure with some focal circulatory disturbance in the brain. So far as the relation of that focal circulatory disturbance in the brain to the area of necrosis is concerned, I feel sure that some kind of organic vascular damage is present. Dr. Lieberman said that there was no evidence of arteriosclerosis of the vessels. Needless to say, in cases of genuine hypertensive vascular disease the large arteries at the base of the brain may appear normal, although the intracerebral arteries will show hyalinosis and other necrotic changes of the walls. One would have to study this brain more closely to be sure what really has led to the localized circulatory lesion. I do not hesitate to say that in this case organic vascular damage was responsible.

Since the work done by Bonhoeffer and by others before and after him, one has had to distinguish between hallucinations and hallucinosis. Many patients who are mentally disturbed and offer psychiatric problems suffer from hallucinations. Other patients with localized lesions in the occipital area show neurological disturbances of vision and suffer from a hallucinosis. There is a distinct difference between hallucinations and hallucinosis. When the clinical syndrome is composed of psychotic elements and focal neurological manifestations, the distinction between the two may be rather difficult in some cases. This patient obviously had had hallucinations, as well as signs of focal lesions in areas 17, 18 and 19. The speaker has discussed the interesting differences in visual disturbances caused by lesions in these different areas. The patient's hallucinations were obviously of different character at different periods of his illness. He went through periods of anxiety, acute intoxication and delirium. It is interesting to question whether the visual disturbances caused by organic lesions in the occipital area had a pathoplastic value. This may be difficult to decide.

Acromegaly Following Surgical Removal of a Chromophobic Adenoma of the Pituitary Gland: Study of a Case. DR. MARTIN H. HALVORSEN, Elgin, Ill.

The patient, a man aged 51, first showed signs of illness at the age of 29. His initial symptoms were anorexia, fatigue and the development of an irritable disposition, followed by petit-mal-like episodes accompanied with vomiting. His condition was diagnosed variously as tuberculosis and hysteria. In 1932 physical examination and roentgenographic studies revealed changes typical of intrasellar tumor with compression of the optic tract and bitemporal hemianopsia. The basal metabolic rate and glucose tolerance were within normal limits. At that time a huge pituitary tumor was successfully removed; studies with hematoxylin-eosin and methyl violet–orange G preparations revealed a typical chromophobe adenoma. Three and one-half years later distinct acromegalic features developed; these are still present. There was marked deterioration of personality, necessitating institutional care. The occipital-mental circumference in 1936 was 58.5 cm.; it is now 68.8 cm. At no time did the clinical picture, dextrose tolerance curve or basal metabolic rate reveal evidence of hypopituitarism. There is no evidence of increasing intracranial pressure. The occurrence of a hyperpituitary state following removal of a chromophobe tumor is apparently unique.

DISCUSSION

DR. JOSEPH LUHAN: Could not Dr. Halvorsen explain these psychotic symptoms by some continuing growth of tumor destroying the frontal lobes. Has there been any attempt to investigate the shape of the ventricles?

DR. PERCIVAL BAILEY: I do not remember seeing this patient. I cannot say from my own knowledge whether he was acromegalic or not, but Dr. Bucy is a pretty good observer. Acromegaly, as you know, is supposed to be due to an increased secretion of the cells—eosinophilic cells or the cells of an adenoma which is composed of eosinophils. Therefore, if this tumor has been eosinophilic, he should have shown signs very early. I looked at the sections of this tumor just a few days ago and, so far as one can tell from hematoxylin-eosin stain, it seemed to be an ordinary chromophobic tumor. One cannot be sure without making special stains. No one will ever know whether the gland at that time was characteristic of acromegaly or not, such granules not having been found at the time. Suppose, as stated, the patient was not acromegalic but became acromegalic later; it becomes a question as to how and what is to explain it. One can suppose that a portion of the gland at any rate or the tumor had been repressed or interfered with by the mass of tumor removed at operation. One knows of such instances in which other functions returned after operation. For example, I had a patient who came to the hospital for removal of an adenoma and who had been amenorrheic for about ten years. She and her husband had become very careless before the operation because of that long period of amenorrhea. After the operation they took no precaution, and she became pregnant. There was a case in which a function had been suppressed and returned, and one can suppose in this case that function had been suppressed by the part of the tumor removed and was resumed afterward. That is pure hypothesis, but it is necessary to explain the facts in this case, which is a very unusual one and, if true, would be entirely unique in my experience.

The Conscious and Unconscious Attitudes of Patients Toward Electric Shock Treatment. DR. SEYMOUR FISHER, V. A.

The study sought to determine patients' conscious and unconscious attitudes toward electric shock during various stages of the treatment procedure and how these attitudes are related to the clinical effects of treatment. Thirty male veterans were intensively interviewed after having received two treatments and again on the completion of 10 treatments. The patients' feelings about all phases of treatment were recorded in detail. In addition, their unconscious attitudes toward shock were studied in terms of their interpretations of a special series of thematic apperception pictures.

The findings were summarized.

1. In general, patients found electric shock treatment very disturbing. This disturbance increased as treatment proceeded.

2. Sixty per cent of the patients indicated that shock stimulated conscious fears of dying.

3. The patients manifesting clinical improvement showed only moderate conscious and unconscious fear toward the treatment. However, those not clinically improved manifested extreme conscious and unconscious fear toward shock.

DISCUSSION

DR. MAXWELL GITELSON: I was especially interested in the indications of a possible correlation between less intense fear or absence of fear and the ultimate improvement. The point should be recalled that there are some patients with a diagnosis of malignant illness who are nevertheless readier for recovery than others with a similar diagnosis. It may be that those patients who have less fear of electric shock treatment have an altogether more benign attitude toward whatever treatment the doctor may have exhibited. It is the capacity of a good relationship with the doctor which makes the prognosis favorable. It would be interesting to carry out a control study in which any other type of treatment than shock therapy is offered and an examination of the question of fear conducted. The same correlation might be found, because the important thing is the attitude toward the physician.

Adrenocortical Function in Mental Diseases. Dr. M. K. Horwitt, Ch.

The development of the concept that the concomitants of stress can produce organic disease and its impact on modern psychiatric thought were reviewed. The present state of knowledge in this field is not sufficient to warrant the hope that pituitary adrenocorticotropic hormone (ACTH) and adrenocortical sterols will have great therapeutic usefulness in the near future. These compounds are important as new tools for the study of stress reactions and may be the forerunners of new methods and new ideas, which the psychiatrist should be prepared to use to his advantage.

Many traumatic situations, such as physical punishment, severe somatic illness and sincere attempts at suicide, have in the past been associated with ameliorative effects on the psychotic state. In recent years, sympatheticoadrenal stimulation of the adrenal cortex has been achieved by many forms of "shock" or stress therapies. Selye's description of the "alarm reaction," with the subsequent development of the "adaptation syndrome," has made it possible to place all these stressful reactions in a common classification.

Correlations of the ketosteroid excretion of schizophrenic patients after administration of a pyrogenic material with their dextrose tolerance curves have substantiated the impression that schizophrenic patients may be divided into three groups, on the basis of whether they gave an overreactive, a medium or a flat response to a stress situation. Such divisions, though definite if obtained on the basis of daily results over a two month period, cannot be made after analyses of only a few samples of blood and urine. At any given time an overreactive patient might be in a temporary state of adrenal exhaustion. Conversely, the unresponsive hebephrenic patient, who usually gives a characteristically flat dextrose tolerance curve, may on some occasions give a normal or high curve.

It was suggested that if shock therapies continue to be correlated with the patients' adrenocortical response, cognizance be taken, in evaluating the course of the therapy, of whether the patient is in the stage of resistance or the "stage of exhaustion."

Frequency and Length of Stimulus in Electric Shock Therapy. Dr. Alexander Hilkevitch, Ch.

The present study was carried out to investigate the optimal frequency, the optimal length of impulse and the optimal interval necessary for a convulsion with the use of a "square wave" stimulator. There were 99 male patients, whose ages ranged from 20 to 35 years. The duration of stimulation was used to measure threshold for each convulsion. The peak amperage was maintained at 250 milliamperes, and the voltage was kept at 110 volts. With a specified intensity of electrical current, the interval was the governing factor in determining threshold. The optimal interval was found to be 3 milliseconds and the optimal impulse was 2 milliseconds. This study indicates that when an electrical current or adequate amperage and voltage is used, a frequency of 200 cycles per second, which combines the above values for interval and impulse, should give optimal results in convulsions. Although this stimulus is longer than is usually suggested for unidirectional shock treatment, the electrical charge is still about one-third that used with the alternating current stimulator.

DISCUSSION

Dr. Alex J. Arieff: Dr. Hilkevitch's physiological experiment is much more important than previous works, in which optimal frequencies have been worked out with alternating current. With alternating current one cannot work any interval; one can figure out the length of the impulse, but even that is not accurate on the basis of frequency. Therefore, one has many authors quoting optimal frequency of currents for stimulation of the brain or nerves, and they have practically all used alternating current. The way in which to do research work with the alternating current would be to have a stimulating machine which could deliver one sine wave and then cut it off and vary the interval. That would be a rather intricate apparatus. I am glad that some one has taken the trouble to work this out on the human subject. So much so-called electric shock research is done by persons who have no concepts of electrical terms; as a result, their deductions are to be doubted. Dr. Hilkevitch has made an important verifying contribution in showing that the interval between square wave stimuli, and not the frequency of stimuli, is the important factor.

PHILADELPHIA PSYCHIATRIC SOCIETY

Theodore Dehne, M.D., *President in the Chair*
Regular Meeting, March 10, 1950

Genetic Differentiation of Schizophrenic, Manic-Depressive and Involutional Psychoses. Dr. Franz J. Kallmann, New York.

The scientifically unproductive nature-nurture controversy in relation to disorders of human behavior, particularly schizophrenia and the manic-depressive psychosis, will cease as soon as it becomes generally accepted that an understanding of the principles of human genetics is indispensable for many diagnostic, therapeutic and preventive purposes of psychiatry.

The need and feasibility of a consistent system of diagnostic classification with respect to schizophrenic, manic-depressive and involutional psychoses are indicated by a comparative analysis of the taint distribution observed in a total of 6,115 blood relatives (parents, siblings and co-twins) of statistically representative samples of psychotic twin index cases (1,232 twin index families). There is no evidence supporting either the popular hypothesis of a genetic relation between the entities of schizophrenia and manic-depressive psychosis (in the sense of interchangeable or somehow complementary genic elements of causation) or their pessimistic relegation to the status of "semantic conventions." It is safe to assume that the mode of inheritance is that of a single recessive in schizophrenia and an irregularly dominant in manic-depressive psychosis. The principal genetic affinity of involutional psychosis is to the group of schizoid personality traits, and therefore at least indirectly to the schizophrenic disease entity, rather than to that of the manic-depressive psychosis.

DISCUSSION

Dr. Earl D. Bond: Dr. Kallmann has challenged the entire progress of psychiatry in America. My own interest was aroused when I saw a family in which both parents had manic-depressive psychosis and the first nine children also had the disease, the tenth, a physician, having no trouble. As I talked to physicians in training for psychiatry, I found that such cases were not uncommon. I was also interested in the work of the only American who had collected records of twins, Dr. Rosenau. I was troubled by the fact that he seemed to collect stories. Then the idea of birth injury idea entered the whole thing, and it was not the work of a geneticist at all. Now, when talking to students about heredity, I generally say, "Read Dr. Kallmann's articles." However, I do not urge any one to believe every word that one reads in any book.

Dr. Theodore Dehne: My chief difficulty in accepting Dr. Kallmann's conclusions is that as time passes I have increasing trouble in differentiating schizophrenia, manic-depressive psychosis and involutional melancholia. They have come to seem more and more alike to me.

Dr. Arthur P. Noyes, Norristown, Pa.: No one has studied as deeply and scientifically the matter of heredity in mental disease and the factor of twins as has Dr. Kallmann. The history of modern knowledge is concerned in no small degree with man's attempt to escape from his previous concepts. The problem of the genes and their relation to us is pretty well summed up in this statement: "The fundamental organization of a person is determined by his genes. He is able to produce an approximate duplication of himself and to grow into the form of a human being. This is modified and extended by what happens to the persons the genes create [Freud]."

Dr. Kallmann's observations in recent years have disturbed me. It is not at all a matter of the genes carrying the trait for male or female, woodchuck or human being. A human being is the result of thousands of processes. It may well be that there is a genetic obstruction, an inability to carry out—for example, a mental deficiency arising from phenylpyruvic acid. This may be the case in some psychoses. One can conceive of it being true in the manic-depressive psychosis, although in this disturbance it may be a biochemical disturbance, perhaps of an identical nature, which leads to behavior of the so-called manic-depressive type. I often wonder whether schizophrenia, or dementia precox is an entity. I must confess I have my doubts about it, and the idea of its being a distinct disease was more than shaken tonight. Is it not possible that, after all, schizophrenia is a pattern of dealing with stresses? The clinical

syndrome is modified largely by the experiences of the individual. It could not exist unless there was the capacity for its development, but the clinical picture as we see it will be general and its specific features will be determined by its pathoplasticity.

DR. FRANZ J. KALLMANN, New York: Tomasin, in Iceland, did not study twins. He provided the one study for the normal population, for a certain population group; in this study he claimed that he found no difference in the incidence of manic-depressive psychoses among the brothers and sisters of patients with manic-depressive disorders and that for a normal average sample of the population. However, according to Tomasin, 7.5 per cent of all persons in Iceland have manic-depressive psychoses. Obviously, such a high average is more likely to be found in dealing with a definitely inbred group. Iceland has only about one-tenth the population of Queens Borough, New York. The Icelanders marry among each other, and Tomasin is not dealing with an average group. I know of no other group with an incidence of manic-depressive psychosis of 7.5 per cent. He has not studied twins at all, although I presume they occur in Iceland.

With respect to the statement that one could not quite classify schizophrenia as an entity, but, rather, might regard it as a pattern of dealing with stresses: In my opinion, these two statements mean precisely the same thing. Schizophrenia is a specific pattern of response to stress, and it is a pattern of response to stress that is available only to a relatively small number of people, meaning that, given a constellation of stress conditions, one can say that there are a number of people who will not respond with a schizophrenic response to that stress. I agree that it is difficult to differentiate between a schizophrenia and a manic-depressive psychosis. Manic-depressive psychosis itself is rare.

Robert A. Bookhammer, M.D., *President in the Chair*
Regular Meeting, April 14, 1950

Forensic Psychiatry and the Psychiatrist in Court.

DR. THEODORE DEHNE: The program committee has felt it was worth while to have a meeting on the subject of forensic psychiatry and the psychiatrist at court. We have brought together a panel of distinguished citizens of Philadelphia to discuss this subject: Dr. Frederick Leavitt, Hon. Gerald F. Flood, Thomas F. McBride, Esq., and Dr. Edward Strecker, with Dr. Samuel Hadden as moderator.

The first speaker is one who has come to be regarded as a true expert, and who in his testimony has at all times been an upholder of the finest tradition of psychiatry, Dr. Frederick Leavitt.

DR. FREDERICK LEAVITT: Frequently, the procedures of law seem to be not justice, but law, because law is fixed and justice is a matter of opinion. What appears to be justice for one side of the case is, by an emotional coloring, not justice for the other side.

When the physician goes into court, he should realize he is there as a guest of the court, and he should conduct himself as a guest and not as an intruder. The psychiatrist in court is there to give of his skill, his knowledge and his experience with relation to the particular case at issue. But it has been my experience that frequently all factors of the special and general examination and its collateral issues are not taken into consideration in arriving at a conclusion in court. This situation is distinctly at variance with the procedure in medicine, that of arriving at a diagnosis when all factors having to do with the case are seriously considered.

When a witness goes on the stand, he holds up his hand and swears to tell the truth, the whole truth and nothing but the truth. But seldom is he permitted to tell the whole truth, because he is interrupted right in the midst of telling the whole truth and is permitted to tell only part of the truth.

In a recent court procedure in which Dr. Strecker and I were working together, we had the privilege of discussing the case with the attorneys for the prosecution and the attorneys for the defense, as a result of which all of the attorneys involved in this particular case, as well as the Court, knew the psychiatric aspects of the case, a situation which made it very

comfortable for all the medical witnesses in that particular court procedure. It also did away with what is commonly known as the "battle of the experts."

HON. GERALD F. FLOOD: Dr. Leavitt has talked very largely about law, which he knows. I am talking to a considerable extent about psychiatry, which I do not know. It is the psychopathic personality with whom we in the courts have our greatest difficulty. The very breadth of the definition shows that the psychiatrist cannot tell us as laymen in advance very much about this person; nor does he tell us very definitely what to do about him. We who are not of the medical profession do not like that. No one likes the other professional man not to be definite; but we know that neither are we definite when we give legal advice.

For the individual psychiatrist I think it means that he should be chary in hazarding his hard-won position as a necessary and extremely important part of the administration of criminal law by claiming more than he can prove to the satisfaction of the educated layman.

We laymen who are judges are going to say, and do say: "If you cannot define this thing more clearly, and it has to be determined by experience only, it will be my own experience as a representative of the community, and not any experience which I get second-hand, that will guide me." Not only are many judges likely to say this, but legislators are apt to say it, and so is the community.

Under the law as it now exists in Pennsylvania—the law that was laid down in the McNaughton case 100 years ago—the only question we have before us in a criminal case when the question of sanity comes up is whether or not the defendant knows the difference between right and wrong. That is the only issue there is legally. If that issue is not decided in the ordinary way by examination, cross examination and all the rest of it, constitutionally the trial may be set aside.

We are getting quite far away from this. In case after case the psychiatrist comes in and testifies as to what is really wrong with this man—not whether he knows the difference between right or wrong—what he is suffering from and what disease he has. The situation is a little odd, for legally this testimony has no significance. Practically, of course, it has very great significance. It is there, I think, that we can begin to jump this constitutional barrier.

In Pennsylvania the jury has an absolute discretion as to imposing life imprisonment or death in a case of first degree murder. If there is a plea of guilty, the court has absolute discretion. We have to depend on the enlightenment of every one concerned with the process.

Psychiatrists ought to resist having courts or lawyers get them into court, first swear them to tell the whole truth and then not permit the psychiatrist to say what he conceives to be the whole truth. If some movement could be started whereby the psychiatrists themselves would take a forward position and insist that courts, while not moving with the same speed as medical science moves, nevertheless should not be back in the days of 107 years ago.

THOMAS F. MCBRIDE, ESQ.: I subscribe heartily to the idea that there should be no psychiatric circus, and that there should be no undignified battle of experts. But I do not see how, as long as our constitution remains what it is, it can ever be avoided that a man shall stand trial for his life or his liberty without being able to summon to his defense any witness, whether that witness be a witness to the offense or a witness who merely gives an opinion which is relevant to the issue involved. Certainly, if there be a qualified medical expert who can and is willing to give an opinion as to a man's sanity or insanity, that is relevant to the issue of criminal guilt.

I do not think the time will come that we can eliminate the necessity of each side's being allowed to produce witnesses as to any such vital issue.

DR. EDWARD STRECKER: In every capital case and in many others, the psychiatrist, the competent, honest psychiatrist, faces a serious dilemma. While it is paradoxical, it is still true to say that if he wishes to leave the witness stand with his professional reputation intact and, more important, with his conscience unviolated, he will have to use some double talk.

Mr. McBride probably will not entirely agree with this, but it is the business of the jury and the judge and the district attorney and counsel for the defense to determine whether this man is guilty or not guilty, that is, whether he did or did not commit the criminal act. At that point the psychiatrist has a most important role, if it would be recognized. He then, as Judge Flood has said, is consulted and might even have a certain amount of authority in instructing the sentencing judge as to this man's degree of responsibility and as to the kind of corrective punishment which would meet the situation.

PHILADELPHIA NEUROLOGICAL SOCIETY

Helena Riggs, M.D., *Presiding*
Regular Meeting, March 3, 1950

Reflex Seizures Precipitated by Immersion in Water. DR. JOHN A. CHURCHILL (by invitation) and DR. MARY L. RUTLEDGE (by invitation).

A brief notation by Wilson and another by Allen are, to our knowledge, the only reported instances of seizures precipitated by immersion in water. The subject of this report was a 1 year old boy who had been well until August 1949. At this time he had onset of seizures which occurred whenever his buttocks were wet.

Within 30 seconds of immersion in shallow water, with a temperature of 60 to 80 F., he would lose consciousness and have a mild, generalized tonic seizure with pupillary dilation, lasting five minutes. Electroencephalographic and electrocardiographic tracings were obtained during two attacks. Shortly after immersion, the electroencephalogram showed a build-up of diffuse high voltage slow waves. Seventy seconds after the appearance of electroencephalographic changes pronounced bradycardia and intervals of apnea began. The blood pressure was increased throughout the attack.

Nothing except wetting the perineum precipitated seizures. Dry cold and heat were ineffectual. Stimulation of the carotid sinus produced no alterations in the pulse. Interpretation of the response is difficult. There is possibly a disturbance of autonomic centers in the diencephalon, so that afferent impulses from cold receptors in the perineum are sufficient to produce an exaggerated response from respiratory, cardioinhibitory, pupillary and conscious centers.

DISCUSSION

DR. FRANCIS M. FORSTER: In cases of reflex precipitation of seizures, especially in the somatic sphere, an element of surprise is frequently necessary. Was the element of surprise necessary in this case? In seizures of the somatic type there is frequently evidence of laterality; that is, the stimulus must be applied always, or more frequently, to one side of the body. Was there any indication of laterality in the precipitating mechanism in this case? Finally, the cardiac slowing demonstrated in this case suggests the possibility of a cardiovascular mechanism, such as the carotid sinus reflex. There are, of course, receptor endings in vessels other than the carotid arteries, notably the femoral arteries. Could such a cardioinhibitory mechanism be indicated in this case?

DR. MATTHEW T. MOORE: Under my care is a girl of 18 years with organic disease of the brain who, whenever she crosses the street and inadvertently strikes the curb with her foot, has an epileptic seizure and falls to the ground. However, if she is prepared and observes some one striking her foot, she does not have an attack. In many cases of reflex epilepsy the element of surprise probably potentiates the sensory stimuli through activation of the hypothalamus.

DR. JOHN A. CHURCHILL: Stimulation of any small area of the perineum on one side or the other did not produce attacks. The seizures in this case differ from most reflex seizures in a number of ways, one being the lack of a surprise element or an abrupt response to a brief stimulus. It is not likely that a peripheral vascular or carotid sinus reflex could in itself account for the attacks, especially since the carotid sinus was not hypersensitive to massage. The loss of consciousness and the occurrence of the seizure before slowing of the pulse by such a long interval was thought indicative of a cerebral origin, although Weiss has presented evidence that in carotid sinus attacks cerebral effects occasionally occur independently of a change in pulse.

Exfoliative Cytological Diagnosis of Lesions in the Central Nervous System. DR. WILLIAM R. PLATT, Camden, N. J. (by invitation).

Primary or secondary malignant tumors or other masses situated in the brain and spinal cord and encroaching on any surface bathed with cerebrospinal fluid can liberate tumor cells or other cellular fragments into this field. Occasionally these free surface desquamations implant themselves to produce metastases on near or distant surfaces of the meninges and ventricles and thereby act as a secondary source of exfoliated cells in the ventricular and subarachnoid spaces.

Furthermore, because of the common neurosurgical procedure of needle exploration and aspiration in the region of the cerebral space-occupying mass (in order to ascertain the presence of a tumor, a localized inflammatory or hemorrhagic process and/or cyst formation in a neoplastic, degenerative or parasitic process), the Papanicolaou technic was applied also to the fluids obtained therefrom. Microscopic specimens of fluid from ventricular, cisternal, spinal and cerebral cysts with normal or pathologic cytological structure were presented. The procedure is offered as another diagnostic adjunct to the armamentarium of the neurologist, neurosurgeon and neuropathologist. The test is not intended to supplant or replace the subjective and objective findings and other diagnostic means utilized by the roentgenologist, neurologist, neurosurgeon or neuropathologist in the examination of a patient with a suspected lesion of the central nervous system.

An Adaptation of the Silver Impregnation Method to Brain Tumor Smears. Dr. F. Cabieses (by invitation), Dr. L. Adamkiewicz (by invitation) and Dr. R. A Groff.

The combination of the smear technic with an accelerated silver impregnation method modified from technics of del Rio Hortega is presented as an aid in the study of the architecture and cytopathology of brain tumors.

Color pictures taken from tumors so treated, showing the general arrangement of vessels, characteristic cells and supporting stroma of the main types of tumors of the nervous system, were presented as a preliminary communication.

The diagnostic value of the method was not discussed.

DISCUSSION ON PAPERS BY DR. PLATT AND DRS. CABIESES, ADAMKIEWICZ AND OROFF

Dr. Robert A. Groff: The practical value of Dr. Platt's investigation of cystic fluid from tumors in which there are tumor cells within the fluid seems to be a warning to the neurosurgeon that he should handle this fluid with care, for he may disseminate the tumor. I see no practical value to its use in the aid of diagnosis of tumors.

Our presentation of the silver staining of smears from brain tumors shows the practical value of this method and opens an entirely new field to the study of these neoplasms. With this method, the entire cell can be seen, the blood vessels studied thoroughly in their relation to tumor cells and their association with blood vessels observed. Thus, the picture obtained is so radically different from the usual slide preparations that considerable experience is necessary in interpreting it. We feel that it has been of considerable help to us in the diagnosis of tumors. As to their differentiation, more experience must be obtained. Its use has given us valuable information, and we feel that in the future, with more experience, it will be a decided aid in the interpretation of tumors of the brain.

Dr. Henry R. Liss (by invitation): My co-workers and I have been comparing eosin-methylene blue smears of tumors of the central nervous system with paraffin sections for eighteen months at the Philadelphia General Hospital. Several pitfalls must be considered: Smeared sections may not be representative; firm tumors may not be included, and recognition of one cell may encourage incomplete diagnosis. These objections are overcome by searching the entire field of several biopsy specimens.

The work cannot be done casually. It requires training. Pathologists accustomed to fixed sections have difficulty in orienting themselves to the study of smears. The diagnosis is made by single cells, with no background to rely on. This technic has been successfully employed for almost 20 years at Columbia University. It is a relatively reliable, rapid diagnostic aid to the neurosurgeon.

Dr. Henry A. Shenkin: The value of rapid technics for histological identification of the tumor while the patient is yet on the operating table, is, from my personal point of view, limited. Such information does not affect operative technic and judgment in the handling of a particular tumor. It is important from a prognostic point of view to have an accurate histological diagnosis promptly, with the emphasis on accuracy. The present methods of rapid fixation and paraffin embedding of tissue permit results within several days, which is usually well within the time allotted one, even by an anxious family. So far, the rapider methods of tissue preparation and histological study do not permit as accurate an interpretation as does the slower paraffin technic.

DR. MATTHEW T. MOORE: At the outset, I wish to express my envy and admiration for the technical beauty of the presentation of the two papers. I am certain, however, that Dr. Platt would not have us believe, nor does he wish to create the impression, that we shall be able to diagnose the specific type of tumor in all cases by means of his method. In considering both papers, it may be said that the presence of the tumor can be established and, in rare cases, the type identified.

In considering the first technic, it must be borne in mind that cerebral tumors often become pleomorphic after exposure to high voltage roentgen therapy or after repeated operations. One must be careful, therefore, in making the diagnosis of a specific type on the basis of merely a few cells, a piece of teased tissue or even a paraffin section. Recently, we studied a large tumor which had been subjected to considerable radiation therapy. Small sections from various parts of this lesion showed considerable pleomorphism, and a diagnosis based on one section of the lesion would have led to an erroneous conclusion. The methods described by the authors are a distinct advance in the determination of the presence of an intracranial space-taking lesion.

DR. L. ADAMKIEWICZ: The technic described can be valuable and diagnostic. It is simple and flexible. It can be applied to tissue cultures and biopsy material. It lends itself to numerous modifications, so that it can be used to bring out any component, such as reticulum, collagen or glycogen, in addition to the desired structures in the tumors of the central nervous system. However, some experience with the method will be required for it to be of help to the surgeon in his surgical problems. The technic is as simple as similarly expedient staining procedures, and in many respects it is superior to most.

DR. HELENA E. RIGGS: Dr. Platt, I should like to know whether you centrifuge your material and whether you find that this distorts your cells to any great degree.

DR. ALEXANDER SILVERSTEIN: About 15 years ago my colleagues and I at Temple University Hospital instituted a method of examination of the spinal fluid for detection of cells as an aid in diagnosis of cerebral neoplasms. This procedure proved of help in several instances, especially in cases of metastatic malignant growths. Unfortunately, for various reasons, use of the method was discontinued after about a year.

DR. WILLIAM R. PLATT, Camden, N. J.: I hoped that I have not conveyed the impression that I believe the examination of these smears will give one the diagnosis of the exact type of tumor. I wish only to say that this technic will enable one, with some cytological diagnostic experience, to determine whether the patient has a neoplastic or a non-neoplastic cytological lesion. It will not by any means determine whether or not one is dealing with any specific type of benign or malignant tumor.

With reference to the centrifugation of material, we have used the aspirated material obtained as such because we believe that one can see better nuclear detail if one fixes the aspirated fluid as soon as one gets it; for instance, it may be smeared out on the slides in the operating room and the slides then immediately immersed in equal parts of 95 per cent alcohol and ether. There is sufficient albuminous matter in the aspirate to give one rapid and good fixation. The slide is then carried through the Papanicolaou or other differential stain, and within six to ten minutes one ought to have a fairly good smear, once the setup has been previously arranged in the laboratory. As I mentioned before, the key to the whole technic is rapid fixation.

DR. F. CABIESES: In writing this paper, we were careful to state that we were not presenting our work as an aid in the diagnosis of brain tumors. For some reason, however, most of the discussion has been on the diagnostic possibility of the method.

The study of smeared tissues requires a different stretch of the imagination to understand the structure under investigation. Pathologists trained to diagnose cerebral tumors from serial sections may have difficulties in interpreting and making a diagnosis from smears. A different mental synthesis is necessary, and that is where the pitfall lies.

Behavioral Alterations Following Lesions of the Medial Surface of the Temporal Lobe. DR. ALFREDO F. THOMSON (by invitation) and DR. A. EARL WALKER, Baltimore.

The present report is a study of the behavioral changes associated with amygdalectomy and other lesions of the temporal lobe. In 11 monkeys (macaca mulatta) bilateral lesions of the medial surface of the temporal lobe were made under sterile operating conditions. The lesion on the second side was usually made six days after that on the first.

Striking temporary change in behavior, consisting in tameness, fearlessness and asocial behavior, was noted after bilateral lesions involving the amygdala uncus or hippocampus. Animals having such lesions were very easy to handle; if placed on a table, they would stay quiet or move little, offering no resistance to being picked up. Sexual activity was diminished, at least during the first two weeks after operation. In 1 animal the maternal instinct seemed perverted.

These characteristic changes gradually disappeared, and by the fourth to the fifth month the animal's behavior had practically returned to its preoperative state. Monkeys with lesions in other parts of the inferior temporal cortex did not show such behavioral changes.

The physiological mechanisms involved are discussed.

DISCUSSION

DR. HENRY WYCIS: These experiments of Dr. Thomson and Dr. Walker not only confirm the findings of Klüver and Bucy but are also more important, since more specific areas are removed. Klüver and Bucy removed larger portions of the temporal lobe, whereas these removals apparently are limited to the amygdalae.

Does Dr. Thomson have any histological controls to show us that only the amygdalae have been removed in these animals?

In 1940 Spiegel, Miller and Oppenheim found that lesions restricted to neocortical areas failed to produce the rage reaction. After electrolytic lesions of the amygdalae in cats, acute rage reactions with hissing, snarling and extreme polypnea occurred. Lesions of the tuberculum olfactorium produced similar changes.

Bard, in his work on cats, also has shown that after removal of the neocortex one cannot produce a sham rage. If the amygdalae and the midline structures were allowed to remain intact, sham rage did not appear; but if one then removed these structures, sham rage appears. This confirms Spiegel's experiments.

I attempted to perform chronic experiments in cats but was unable to keep the animals alive for a prolonged time, owing to the acute rage reactions and the high respiratory rate which would occur periodically.

DR. HELENA E. RIGGS: This work is interesting in the light of certain pathological changes. We found in our patients with dementia paralytica who showed pronounced mental changes such involvement of the region of the hippocampus, particularly the nucleus amygdalae, that it became routine to make sections throughout this area. It was usually found to be the most intensely affected area of the cortex, with even more involvement than the orbital surface of the frontal lobe. What that proves I am not sure, but it is interesting that in pathological lesions with mental changes this part is also involved.

DR. HENRY A. SHENKIN: I believe one is on dangerous ground when ascribing emotional and personality changes in animals to a specific cerebral lesion. I believe there can be seen general changes in affect following craniotomy with destruction of varied areas of the cerebrum, which last for a longer or shorter time.

I do not quite understand what Dr. Thomson said with regard to the number of animals operated on and in how many the emotional changes which he described occurred.

DR. ALFREDO F. THOMSON: In six or seven.

DR. HENRY A. SHENKIN: That would hardly be a statistical basis. It would be dangerous, I think, to assume that the lesion was specific.

DR. ALFREDO F. THOMSON: We have no explanation of the difference in the results of removal of the medial temporal gyrus in cats and monkeys. Perhaps it may be correlated with the relative influence of sympathetic activity in cats and monkeys, but the interrelationships are obscure.

The gross findings suggest that lesions of the nucleus amygdalae are responsible for the taming effect, but this conclusion may not be borne out by the histological controls. Bilateral involvement of the amygdaloid complex seems to be necessary to produce the syndrome, for in those animals in which the lesion damaged the uncus unilaterally we did not observe any change. In our series, lesions sparing the uncus did not produce the taming effect. Bucy and Klüver reported similar findings, and their extrauncal lesions were much larger than ours, sometimes being practically a temporal lobectomy.

Helena E. Riggs, M.D., *Presiding*
Regular Meeting, May 5, 1950

Dermatomyositis: Report of a Case. DR. SAMUEL A. ZERITSKY.

Dermatomyositis is a representative member of the collagen diseases, which include rheumatoid arthritis, periarteritis nodosa, lupus erythematosus disseminatus and scleroderma. An abnormal phase of the "alarm reaction" results in disease of the ground substance and involves therefore the hyaluronate-containing tisues. These diseases can occur only when the adrenal cortex is intact. Adrenocorticotropic hormone (ACTH) and cortisone (17-hydroxy-11-dehydrocorticosterone) are capable of reversing the active phases of this whole group of diseases.

The case reported is that of a single woman aged 21 whose illness was preceded by a disappointment in love and an attack of infectious hepatitis. At first she noticed difficulty in alighting from trolley cars. Weakness of the lower extremities progressed, spreading to the upper extremities. She became emaciated and presented areas of pigmentation over the arms, the lower part of the abdomen and the face. A biopsy specimen taken from the shoulder region revealed atrophy of the epidermis, hydropic degeneration of the basal cells and fibrinoid changes in the corium with perivascular lymphocytic infiltration and some serous degeneration of fat cells. Occasional muscle fibers showed degenerative change and were devoid of cross striations.

The Exton-Rose dextrose tolerance curve exhibited a subsequent rise after the second dose of dextrose. Other indexes of function of the adrenal cortex were suggestive of abnormality, and negotiations are in process for treatment of this patient with ACTH and cortisone.

DISCUSSION

DR. HELENA RIGGS: I have never seen a case of this type. The collagen diseases we have seen at the hospital have been of interest to me because of possible involvement of the nervous system in the vascular changes. We have examined the cases of lupus erythematosus and those of periarteritis nodosa. So far it is only in the cases of periarteritis nodosa that I have found any of the characteristic changes in the vessels of the brain. I should be interested if Dr. Zeritsky has any information on the changes in the central nervous system.

DR. MATTHEW MOORE: Dr. Zeritsky stated that he had not seen mention of the collagen diseases made by neurologists. Collagen diseases have been known to neurologists for some time, notably disseminated necrotizing panarteritis or periarteritis nodosa. Dr. Winkelman and I reported such a case two years ago, in which there was involvement of the meningeal vessels and the vessels within the brain substance.

About three years ago there came under my care a man aged 46 who had diffuse dermatomyositis, similar to the condition in the present case. Just prior to that, I had the privilege of treating a patient with scleroderma who had sclerodermatous involvement of the esophagus. He also had difficulty in breathing, and studies showed evidence of involvement of the diaphragm.

DR. SAMUEL ZERITSKY: In my brief review of the literature on dermatomyositis, I came across a case in which the retina was reported to have been involved. At the moment, I know of no report indicating that the brain had actually been studied for evidence of lesions.

It is true that collagen diseases have been described as a syndrome of clinical importance to neurologists. However, the suggestion that dermatomyositis may be based on adrenocortical dysfunction is a comparatively recent development. I have heard that ACTH produces excellent results in cases of scleroderma, a related disorder, and I hope to be able to arrange for a quantity of the drug to be administered to the patient whose case is presented here.

Lipoma of the Corpus Callosum: Survey of the Literature and Report of Two Surgical Cases. DRS. ROBERT A. GROFF, C. T. LIU (by invitation) and ROBERT L. LEOPOLD (by invitation).

Lipoma of the brain is a pathological curiosity. The commonest site for its occurrence is in the corpus callosum. Although there are several reports in the literature of cases with autopsy, only three are reported in which the patients had the benefit of surgical intervention. For this reason, two cases are reported here.

A woman aged 36, a known epileptic, was admitted to the Philadelphia General Hospital because of personality changes. A small lump on the front of the head had been removed at the age of 6 months. At the age of 3 years she began to have generalized convulsive seizures, which continued intermittently until she was admitted to the hospital. A roentgenogram of the skull showed a dense, calcified mass at the center of the anterior fossa. A craniotomy in the right frontoparietal area revealed a lipoma of the corpus callosum. The patient died six days after operation.

The second patient, a white man aged 21, was admitted to the Graduate Hospital for study of convulsive episodes, which he had had for the preceding eight years. There were no localizing symptoms or signs. Plain roentgenograms of the skull showed a few linear calcifications. A pneumoencephalogram revealed a pronounced deformity of the ventricular system, spreading of the bodies of the lateral ventricles and calcifications in the region of the corpus callosum. The tumor was approached along the falx after a craniotomy in the right frontal area had been performed. A large tumor was found and removed. Histologically, the specimen contained mainly fat tissue. Recovery from the operative procedure was uneventful. He has been much improved in the 26 months since operation.

It has been the feeling of most authors that if a diagnosis of lipoma of the corpus callosum, or, indeed, of any tumor of the corpus callosum, is made prior to operation surgical intervention is contraindicated. However, it is my feeling that lipoma of the corpus callosum can be attacked surgically with good results if care is taken to avoid entering the third ventricle and as conservative removal as possible is carried out.

DISCUSSION

DR. ROBERT GROFF: When a neurosurgeon is confronted with a lesion of the brain, he thinks of two things primarily: whether or not he can cure the patient and whether he can produce this cure without morbidity.

Tumors of the corpus callosum in the form of lipoma represent slow-growing congenital lesions. They are in most instances associated with convulsions. When they become large enough, they obstruct the ventricular system and cause increased intracranial pressure. When they have reached this stage, they are operative lesions.

From our experience in the operative treatment of these tumors, particularly that gained in the second case, it would seem that one can operate on these lesions and prevent them from becoming a surgical necessity. By removing the contents within the capsule of the tumor, the size of the lesion is decreased sufficiently to prevent its obstructing the ventricular system. Since the tumor grows slowly, this will carry the patient along for many years. It is for this reason that we feel more optimistic than do List and his co-workers, who express the opinion that these tumors are inoperable.

DR. MICHAEL SCOTT: Has Dr. Groff found any lipomas elsewhere in the nervous system in his cases? In the next case of lipoma of the spinal cord that I see I shall have an encephalogram made to rule out the possibility of lipoma in the cerebrum.

I agree with Dr. Groff that when the classic encephalographic pattern is not found, exploration should be carried out to establish a diagnosis but that no attempt should be made to remove the lesion completely, because of danger to the anterior cerebral artery.

DR. SAMUEL LEOPOLD: In answer to Dr. Scott's question, I found no evidence in the literature of any associated lipoma, but attention has always been concentrated on the corpus callosum, and I do not think it fair to assume that the rest of the nervous system has always been explored adequately.

Solitary Calcified Intracranial Tuberculoma; Report of Case with Postoperative Survival of Fourteen and One-Third Years. DR. ISADORE ROSE (by invitation).

A case of solitary intracranial tuberculoma, which was removed surgically, was reported. The patient, a Negro girl aged 17 at the time of operation, had had right-sided jacksonian convulsions since the age of 9 years. Prior to operation a roentgenogram of the skull revealed a calcified mass on the left side. The mass, which was removed at operation, weighed 16 Gm. and proved to be a tuberculoma. The patient survived 14 ⅓ years after operation.

The only extracranial tuberculous foci demonstrated were tuberculous lymph nodes in the peritoneal cavity, shown at necropsy. The brain showed no evidence of inflammation or scar formation.

Calcification within an intracranial tuberculoma is relatively rare. It presents a fairly characteristic roentgenographic appearance, having a homogeneous center and a serrated, angular margin. A review of the literature reveals only 26 previously reported cases of calcified intracranial tuberculoma. However, the over-all occurrence of intracranial tuberculoma is not infrequent.

There is no persistent agreement as to whether solitary or multiple tuberculomas are the more frequent. The diagnosis of tuberculoma should be borne in mind when there is roentgenologic evidence of intracranial calcification, particularly in solitary lesions which might be amenable to surgical treatment.

DISCUSSION

DR. CHARLES RUPP: Dr. Rose's case is interesting particularly from the standpoint of the survival of the patient in reasonably good health, except for her seizures, for 14 years. While most patients with tuberculoma succumb within an average of six to nine months, a few live much longer. Dandy has cited a case of survival for over 20 years. In both these cases the operation was done in the prestreptomycin era, and the tendency to long survivals in a few cases must be considered in evaluating the benefits of streptomycin.

In this case the tuberculoma was calcified. Contrary to the statement frequently made, calcification of tuberculomas is not very common. In our series of 82 lesions, only two were calcified.

DR. RUDOLPH JAEGER: It should be emphasized that not all patients with tuberculomas die at the time of operation. I have removed two tuberculomas, with recovery of both patients. One of the tuberculomas was calcified; the other was not. The one that was calcified was operated on about two years ago. The child came in, not with symptoms of tumor but with signs of mild meningitis. While I was treating the youngster for suspected aseptic meningitis, the roentgenogram of the skull showed a calcified spot between the temporal and the frontal lobe. I suspected it was a tuberculoma and treated the lesion on that basis. Streptomycin was administered over a long period—perhaps two months. Craniotomy was then performed, and the child has since been quite well and afebrile.

A patient with a benign tuberculoma should be operated on; the risk should not be great. Perhaps streptomycin has added something to present day therapeutic methods.

DR. ISADORE ROSE: In looking through the literature on this lesion, I was surprised at the paucity of reported cases. There were only 26 reported cases of tuberculoma showing calcification.

Relief of Thalamic Pain by Mesencephalotomy. DRS. F. MURTAGH JR., H. T. WYCIS and E. A. SPIEGEL.

A man with hypertensive vascular disease experienced transitory hemiparesis and hemianesthesia on the right side in 1946 and a similar episode on the left side in 1947. In both episodes there was rapid recovery from the paralysis. However, on the third day of the second attack severe, sharp pain appeared in the left side of the face near the outer canthus of the eye. This pain became progressively worse and was subject to sudden, severe, lightning-like exacerbations. Other physicians, attempted to relieve the pain by alcohol block of the left supraorbital and maxillary nerves, retrogasserian neurotomy (left side), electric shock treatments, resection of the cortical sensory face center on the right side and excision of the left prefrontal lobe. These measures proved ineffective except for the retrogasserian neurotomy, which produced complete, permanent anesthesia of the field of the left trigeminal nerve and relief of pain for five hours. After bilateral mesencephalotomy, performed with the use of local anesthesia (electrolytic destruction of the spinothalamic and quintothalamic tracts in the midbrain), the pain disappeared completely. Three and one-half months later there was only very slight pain; the sole complaint was diplopia and loss of taste. It is inferred that afferent impulses carried by pain-conducting pathways play an important part in the genesis of thalamic pain.

DISCUSSION

DR. E. A. SPIEGEL: In rare cases relief of thalamic pain has been attempted (Frazier and Lewy by chordotomy; Baudouin and Puech, by injection of cocaine; David, by electrocoagulation of the ventroposterior portion of the thalamus). Walker tried mesencephalic tractotomy; the patient died the next day, so that the possible effect of this operation is not known. We attempted interruption of the spinothalamic and trigeminothalamic tracts in the midbrain by the less hazardous stereotactic method. Whether the relief will be permanent, we do not know; but we may at least infer that interruption of the long pain-conducting tracts may relieve thalamic pain for some time and that centripetal impulses play an important part in its genesis.

DR. HENRY WYCIS: In trying to interrupt the spinothalamic system in the midbrain, one usually uses Walker's approach, which necessitates a major craniotomy with dislocation of the occipital pole. In two instances in which I attempted it there was one death. Both Sjöquist's patients died after such a procedure.

In operation for mental disorders, one has rather large structure, such as the dorsomedial nucleus, to injure, but the spinothalamic system in the midbrain occupies only a few square millimeters, so that extreme accuracy is required. Recently we have performed necropsy in one of our cases of carcinoma in which a lesion had been made on the left side of the midbrain for the relief of intractable pain in the arm. A well circumscribed lesion had been placed accurately in the left spinothalamic tract.

DR. JOSEPH YASKIN: I wonder why the authors did a bilateral operation in this case of unilateral pain. I am sure they had a good reason for it.

DR. HENRY SHENKIN: Dr. Wycis touched on the accuracy with which one must place this lesion. My own experience with stereotactic apparatus is limited, but I know that except in the rat and the cat I was unable to be accurate with stereosections in more than 50 per cent of cases. I wonder how accurate one can actually be in human material.

DR. ANTHONY TORNAY: I have a patient, a white man aged 47, who had right hemiplegia. His vascular lesion occurred several years ago. Since that time he has apparently recovered some motor power, and also some sensation in the right side of his body. He has spasms of his extremities, and with these spasms he has terrific pain in the entire right side of the body. Dr. Shenkin and I have wondered what effect an excision of the prefrontal lobe would have. The patient has already made one attempt at suicide because his pain is so severe.

In the authors' paper there is mention of failure of prefrontal lobotomy in the case presented. Do the authors know of other cases in which this operation has failed? How would they propose to manage this particular patient?

DR. WILLIAM WHITELEY (by invitation): Four days ago we did a prefrontal lobotomy on a man aged 50 who had thalamic pain of three years' duration. It began two hours after a sudden hemiplegia, remained constant and debilitating and was confined to the hemiplegic side. Prior to operation, he had had spastic left hemiparesis with choreic movements, left homonymous hemianopsia and normal sensation. Flattening of personality followed lobotomy, and he appeared comfortable. Occasionally he admitted pain, but with inappropriate calmness. Interestingly, the spasticity and choreiform movements disappeared. It is too early to report a cure in this case.

DR. CHARLES RUPP: Have the authors any explanation as to why mesencephalotomy should have been effective after practically every other pain-deadening procedure was unsuccessful? I should be interested in hearing their physiological explanation.

I should also like to ask about the mental status of the patient at the present time. One wonders whether there is any possibility that there might be a psychological element in his pain and whether he is now so vegetablized by the shock and other procedures that he is less conscious of any form of sensation.

DR. HENRY SHENKIN: With respect to relief of thalamic pain with lobotomy, at the Graduate Hospital we have had three experiences with lobotomy for a complete thalamic syndrome involving the entire side. One of the patients died after operation and was never well enough for us to decide whether he was better. The other two had a remarkably good result. The longer postoperative period is now about eight months, and the patient is without complaint.

DR. MICHAEL SCOTT: Was the lobotomy bilateral or unilateral?

DR. HENRY SHENKIN: Unilateral frontal lobotomy.

DR. ERNEST SPIEGEL: Mesencephalotomy was performed bilaterally because the spinothalamic systems carry crossed and uncrossed pain impulses. Thalamotomy does not significantly change the pain threshold, but in cases with a definite emotional hyperreactivity to the pain combined mesencephalotomy and thalamotomy may be beneficial by interrupting the main pain-conducting systems, as well as reducing the emotional reactivity to remaining pain impulses.

None of the existing theories of thalamic pain seems satisfactory. Cortical inhibition of thalamic activity could not be proved. But whether one inclines to Wilson's or to Foerster's theory, pain-conducting systems should play a role and relief should be expected from their elimination.

After the unilateral prefrontal lobotomy, the patient's work was not as accurate as before.

In Dr. Tornay's case, the first question is whether the pain and spasm always appear simultaneously.

DR. ANTHONY TORNAY: They appear at the same time.

DR. ERNEST SPIEGEL: Do you think the pain is part of or independent of the spasm?

DR. ANTHONY TORNAY: We gave him mephenesin (tolserol) to see whether or not we could eliminate the pain, but it had absolutely no effect on him. We gave him quinine experimentally to see what might happen; there was no effect on his spasm or pain. We felt that the amount of spasm was not sufficient to cause the pain he complained of and that the pain and spasm were a part of the same syndrome.

DR. H. T. WYCIS: Since 1936 we have done stereotactic work on animals in Dr. Spiegel's laboratory. When we tried to apply this experience to human subjects, it became apparent that any method relying on the shape of the skull is not accurate. We use, therefore, as a landmark the pineal body or the posterior commissure. The variability in the relationship of the structures in the brain stem to these landmarks is rather slight. The accuracy of stereoencephalotomy has been greatly increased by an attachment permitting one to mark the position of the apparatus by tattoo marks and to reapply it in exactly the same position at operation.

PHILADELPHIA NEUROLOGICAL SOCIETY AND NEW YORK NEUROLOGICAL SOCIETY

Helena E. Riggs, M.D., and Lewis D. Stevenson, M.D., *Presiding*

Joint Meeting, April 21, 1950

Neurological Sequelae of Measles. DR. AXEL K. OLSEN, Sayre, Pa. (by invitation).

A brief report of six cases of involvement of the central nervous system following measles was presented. They were felt to be of interest because at onset three had been considered to represent a purely myelitic syndrome. The only adult in the group died within a few hours after onset of his disease, with signs of bulbar involvement. The second of the three patients presented no definite symptoms or signs during the acute phase of the disease, and the involvement of the central nervous system in her case was apparent only after she had become ambulatory. The third patient presented the usual clinical history and signs of acute myelitis and recovered completely. The remaining three patients presented typical pictures of diffuse disease of the central nervous system, with apparently complete recovery. All cases appeared during epidemics of regular measles in a relatively small community. The involvement of the central nervous system appeared usually at the fifth to the seventh day of the disease except in one case, in which it was evident ten days after the onset. Routine laboratory study showed nothing significant. Examination of the spinal fluid, performed in five cases, revealed an increased cell count in two and an increased total protein content in three. The spinal fluid was normal in the one fatal case. Treatment was supportive in all instances.

DISCUSSION

DR. IRVING SANDS, Brooklyn: It was with pleasure that I listened to Dr. Olsen's presentation. In 1943 we reported 56 cases of measles encephalitis (Litvak, A. M.; Sands, I. J., and Gibel, H.: Encephalitis Complicating Measles, *Am. J. Dis. Child.* **65**:265-295 [Feb.] 1943), with follow-up studies in 32. Measles encephalitis, like the encephalitides complicating the other exanthems, is really a meningoencephalomyelitis. The following classification was based on the preponderance of symptoms:

1. Meningeal type—characterized primarily by classic signs of meningeal irritation, such as nuchal rigidity and bilateral Kernig and Brudzinski signs (6 cases).

2. Encephalitic type—characterized clinically by convulsions, coma, disturbances in the deep reflexes and the presence of pathological reflexs (35 cases).

3. Bulbar type—characterized primarily by disturbance in cranial nerves, difficulty in swallowing and respiratory and cardiac disturbances (2 cases).

4. Striatal type—characterized primarily by disturbance in muscle tonus and by the presence of abnormal involuntary movements (2 cases).

5. Myelitic type—characterized primarily by disturbance of deep reflexes and muscle tone and possibly by sensory change (1 case).

6. Mixed type—characterized by a combination of the foregoing symptoms (10 cases).

Anatomically, the chief lesion was in the white matter, and areas of demyelination were the characteristic microscopic feature. Onset of the encephalitic complications in measles occurred generally between the fourth and the sixth day after the appearance of the measles rash. Sixty-nine per cent of the 56 patients studied presented serious neuropsychiatric complications. At first the neurological signs and symptoms predominated, but with the passing of time the psychiatric problems assumed priority, with behavior disorders of various types, both at home and at school. Persons with light skin, particularly those with blond or reddish hair, contributed the largest number of encephalitic reactions. Patients with a high spinal fluid cell count were less likely to present complications than those whose spinal fluid showed very little cellular reaction. Our study convinced us that measles encephalitis is a most serious complication, with crippling neurological and psychiatric residua.

Herniations of the Cervical Intervertebral Disk and Scalenotomy. DR. HENRY A. SHENKIN and DR. ROBERT A. GROFF, Philadelphia.

Four cases of presumed lateral herniation of a cervical intervertebral disk relieved by scalenotomy were reported. The diagnosis was made on the basis of findings in the roentgenograms of the cervical portion of the spine, and of myelograms in two of the four cases.

Scalenotomy was carried out in one case because the patient was too poor an operative risk for laminectomy and her pain was uninfluenced by conservative treatment. In two cases the pain in the upper extremity was intractable to conservative treatment, yet not severe enough for the patient to consent to a major surgical procedure. The anterior scalene muscle was sectioned in the fourth case only after the failure of a decompression laminectomy to relieve entirely the pain due to the verified laterally herniated cervical disk.

It is suggested that the syndrome due to a laterally herniated cervical intervertebral disk and that to compression of the brachial plexus by the anterior scalene muscle are not necessarily mutually exclusive.

DISCUSSION

DR. IRA COHEN, New York: I have discussed this problem with my colleague, Dr. Sidney Gros, who told me of two experiences he had had, one in which he removed a cervical disk for the relief of pain, which had persisted after a scalenotomy done elsewhere. In the other case Dr. Gross had removed a protruding cervical disk, without relief of pain, and subsequently performed scalenotomy, which did relieve the pain.

The authors refer to the suggestions in the literature that root irritation may cause spasm of the scalene muscles. The nerve supply for the anterior scalene muscle comes from the anterior roots just outside the intervertebral foramen, and this may be a reason for the spasm of the muscle, a condition which may be compared to the cramps that are seen, not infrequently, in cases of lumbar herniations.

Within the limitations placed on this procedure by the authors, I believe they have offered us an operative approach that is well worth while. In their cases there was tenderness over the scalene muscle. Procaine may be injected into the muscle to see whether this relieves the pain; it is probable that it will be more effective in cases in which the pain is more widespread than would be expected from pressure on a single nerve root.

DR. HAROLD LEE RILEY, Lynchburg, Va.: Did the authors have any failures?

DR. HENRY SHENKIN, Philadelphia: We have not yet. Frankly, we have not done very many scalenotomies, but they have all been successful. Perhaps Dr. Groff has had some other experience; we have not used the method extensively.

DR. JOHN E. SCARFF, New York: I should like to point out, if I may, that it is common experience to find myositis in the muscles of the upper limb girdle with any pathological process involving the cervical portion of the spine. It is also generally known that the myositis produced by the muscles of the superior limb girdle produces pain reaching down the arm as far as the digits that can easily be mistaken for the pain of root compression due to an intervertebral disk.

I should like to point out in the last case cited that the pain was referred to the eighth cervical dermatome, that the reflex change, namely, loss of the triceps jerk, involved the seventh cervical segment and that the roentgenologic findings should show involvement of the sixth cervical root.

I wonder whether the condition under discussion is not a simple scalenus anticus syndrome, uncomplicated by a cervical herniated intervertebral disk, but with the picture confused a bit by bony ridges appearing in the roentgenograms.

DR. ROBERT A. GROFF, Philadelphia: In Philadelphia we are particularly aware of the anterior scalene syndrome, since Dr. William Bates has been instrumental to such an extent in advancing our knowledge concerning its features. In all the patients who were treated by section of the antertior scalene muscle, a preliminary injection of procaine into the muscle was performed in order to test the effectiveness of such therapy. In all these patients a satisfactory result was obtained by injection. It was for this reason that the section of the muscle was performed.

Dr. Scarff asks whether or not in the fourth case there was pressure on the eighth cervical nerve root; we did not observe such a condition at operation. The patient had definite arthritic changes, and it is conceivable that the pressure on the eighth nerve root was due to the bony proliferation. However, the fact that an excellent result followed section of the anterior scalene muscle would seem to me to rule out compression of the eighth cervical nerve root.

In all our patients, the predominating clinical picture was pain without particular evidence of neurological signs. For this reason, we felt safe in doing a minor operation. If, on the other hand, there is evidence of destruction of a motor nerve root or of pressure on the spinal cord, direct attack should be made on the lesion and not on the anterior scalene muscle.

Psychomotor Epilepsy. DR. FRANCIS M. FORSTER, Philadelphia.

Therapeutic results in cases of psychomotor epilepsy were surveyed. Prior to the advent of phenylacetylurea (phenurone®), 17 of 25 patients with psychomotor epilepsy had their attacks controlled by diphenylhydantoin, phenobarbital or mesantoin® (methylphenylethylhydantoin) Diphenylhydantoin and phenobarbital were the most important. After the advent of phenylacetylurea, 26 patients were given short trials of diphenylhydantoin and phenobarbital, and on this regimen eight had their epilepsy controlled. (The condition of one third to two thirds of the patients with psychomotor epilepsy can be greatly improved by the use of standard anticonvulsants. The range in improvement is dependent on the degree to which the standard anticonvulsants are pushed.) Nineteen patients received phenylacetylurea, and the seizures were controlled in 13. However, four became psychotic, and the drug had to be withdrawn. Five patients with psychomotor epilepsy and electroencephalographic foci in the temporal lobe were treated surgically. Medical therapy had failed in all five. In three of these patients psychomotor seizures were controlled by temporal lobotomy or lobectomy; one died of a brain tumor, and the fifth has not been followed for a sufficient length of time.

Patients with psychomotor epilepsy should be placed under treatment with the standard anticonvulsants, and if these fail phenylacetylurea therapy should be instituted, with due regard to the toxic possibilities. In cases of psychomotor seizures and persistent electroencephalographic foci in the temopral lobe in which standard and new medications fail, the focus in the temporal lobe should be excised.

DISCUSSION

DR. H. HOUSTON MERRITT, New York: Dr. Forster has given us in a short time a complete review of the problem of psychomotor epilepsy. He has shown that it is important to differentiate this type of seizure from other types, owing to the fact that the medication which is effective in one type of seizure may not be effective in another.

My colleagues and I have used phenylethylurea in approximately 100 cases, and we have not been able to control any patient completely with the drug. Some of the attacks were reduced in frequency, but in no case were they completely controlled. We feel that a drug to be really worth while should completely control the seizures. Our incidence of improvement was 32 per cent, which is considerably less than Dr. Forster's. Our average dose was 2.5 Gm., and doses as high as 4 Gm. were given. Gastrointestinal symptoms were the commonest side effects. They are probably related to a disturbance in function of the liver. There have been fatalities from hepatic destruction. In a disease which of itself is not fatal, the use of a drug which may give a mortality rate of even as low as 1 per cent is hardly justified unless the drug is a real miracle worker. I am afraid that Dr. Forster and the rest of us who are working on the problem of psychomotor epilepsy will have to search for a more efficient drug.

DR. FOSTER KENNEDY, New York: There seem to be three types of seizures for which the organic cause, if it exists, is always found in the temporal lobe.

There is an affinity, I think, between the attacks which Dr. Forster has considered and the prolonged attacks of hallucinations with which all are familiar and which have been called "temporosphenoidal fits." There are also attacks, minor to these, in which there is not a loss of consciousness but a change in the stream of consciousness. Sometimes the stream of consciousness is raised so that the patient has an acute sense that he knows what is about to happen. He also has a peculiar sense of the identity of the present with the past, which the French term *déjà vu*.

The distinction between petit mal and the form which Dr. Forster is talking about is not very clear. I am not sure that these attacks are not in the nature of petit mal, which, after all is only a fragment of the great fit, just as fragmentation of a great many other phenomena appears in the experience of the neurologist. The great fit would seem to be due, as was thought long ago, to a complete, sudden mesencephalic block, with loss of consciousness. Psychomotor epilepsy would seem to be a focal fit with, however, a kind of loss of consciousness which is unusual in a focal fit. Focal fits, of course, can go into unconsciousness, but that is not their primary characteristic.

Dr. Forster mentioned the appearance of a temporal tumor of malignant type after years of epilepsy. That has also been my experience; so I have come to look on every case of epilepsy as a potential case of brain tumor.

DR. FRANCIS M. FORSTER, Philadelphia: I feel that the differentiation between petit mal and psychomotor seizures is not very difficult. Petit mal attacks are those which occur in children. Psychomotor seizures occur mostly in adults. Petit mal seizures as a rule occur very frequently, oftentimes many in a day. Psychomotor seizures are incidents not unlike those of a major convulsion. The duration of the individual attack is different. Petit mal seldom lasts more than 30 seconds or a minute. A psychomotor seizure is a matter of minutes. Furthermore, there are electroencephalographic distinctions, and response to therapy is different.

Increased Intrathoracoabdominal Pressure as a Factor in the Paraplegic States. DR. SAMUEL B. HADDEN, Philadelphia.

Unusual increases of intrathoracoabdominal pressure cause many minor and serious cerebral complications. Giddiness, tinnitus, convulsions, coma, hemiplegia and focal cerebral symptoms are often induced by cough and strain. Increased intrathoracoabdominal pressure cuts down the

venous return to the heart, and hence its minute volume output. In addition, it displaces blood into the vertebral and cranial veins. In conditions in which the increase is chronic, the cerebral and spinal congestion induced may initiate progressive degenerative changes, with gradual production of combined cerebral and spinal cord symptoms. Acute neurological lesions may occur suddenly in partially devitalized nerve tissue and mask the chronic disease. Much of the weakness and disability in asthma and emphysema may be due to neurological changes, rather than exclusively to the respiratory-circulatory disturbances.

DISCUSSION

DR. JOHN SCARFF, New York: Dr. Hadden has offered an interesting theory for the pathogenesis of many diffuse small lesions of the brain and spinal cord which result in paralysis agitans and partial paraplegia. However, I believe that many of you share my desire to have Dr. Hadden document a bit more fully the various steps in his thesis. I am interested to know, Dr. Hadden, whether there is any statistical evidence indicating a higher relative incidence of disease of the nervous system, particularly paralysis agitans and partial paraplegia, among miners than among other industrial groups or among the population as a whole. I was unable to get any information regarding the incidence of paralysis agitans in miners from my colleagues in New York. I discussed the problem with neuropathologists, a clinical neurologist and chest specialists to see whether there is a high incidence of parkinsonism or chronic demyelination of the spinal cord in patients with chronic bronchitis and emphysema. All stated that there was not.

I was also interested in the effects of venous congestion of the central nervous system in another group, namely, that with chronic idiopathic epilepsy. Even at the end of a lifetime of convulsions paralysis agitans or disease of the spinal cord did not characteristically develop in those persons.

It would be interesting to put this proposition to an experimental test. It ought to be relatively easy, by graded ligations of the jugular veins, to determine whether induced venous stasis would bring about those changes in the brain which Dr. Hadden hypothesizes.

DR. SAMUEL HADDEN, Philadelphia: I have asked these same questions. Continued observation will give the answers, and there is need for further experimental work. Increased intrathoracoabdominal pressure may contribute to development of paralysis agitans and other lesions by circulatory disturbance. Shunting of blood into vertebral and cranial systems, with resultant stasis, may initiate histanoxic change.

In asthma and emphysema the combination of the forceful expiratory phase and disturbance of oxygenation of blood may be factors in producing degenerative changes. In chronic bronchitis the infectious process and stasis are important. The brief period of strain in epilepsy, as compared with that in emphysema, accounts for the absence of these changes in epilepsy.

Regeneration in the Spinal Cord of the Cat and Dog. DR. W. F. WINDLE (by invitation) and DR. W. W. CHAMBERS (by invitation), Philadelphia.

In experiments to determine the site of action of a purified bacterial pyrogen (pyromen®), cat and dog spinal cords were transected at various levels. After administration of the pyrogen for eight to 61 days, the transected region was stained by the pyridine-silver method.

Cords of animals living 42 days or more after transection revealed clearcut evidence of new growth of neurons into or across the cut. There was some connective tissue scarring between severed ends, and the usual amount of retrograde degeneration was observed. However, there appeared to be no glial scar barrier cut, rather, a blending of the connective tissue with parenchyma of the spinal cord. It was through such regions that nerve fibers could be seen growing into the scar. Numerous blood vessels were observed at the scar-cord junction, and many macrophages occupied spaces between strands of non-nerve cells and nerve fibers in the cord. Along the strands many nerve fibers penetrated the scar or invaded the other cut end of the spinal cord. By following the nerve fibers through serial sections, one could see that they were derived from severed or injured nerve roots, vascular and meningeal nerves and intrinsic cord neurons. No functional regeneration was obtained. Controls showed no regeneration.

DISCUSSION

DR. LEO DAVIDOFF, New York: About 25 or 30 years ago Ramón y Cajal, with his usual superb experimental technic, demonstrated in various laboratory animals that a severed spinal cord makes a very feeble attempt at regeneration, and that in the course of a short time this attempt is frustrated by the formation of connective tissue and glial scars.

A number of investigators in the last quarter of a century have attempted to put the same question to experimental tests, and they have been able to show anatomic signs of regeneration, and even functional improvement or partial restoration, in accordance with their interpretation of their experiments.

Encouraged by this, about two years ago Dr. Ransahoff and I set ourselves very rigid criteria and attempted to demonstrate the possibility of regeneration of the spinal cord in adult cats; we failed. From our data we were unable to show anything that we could interpret as regeneration.

Dr. Windle and Dr. Chambers, by the use of a chemical stimulant, have obtained results which cannot be questioned; they have demonstrated that nerve fibers do cross the sectioned cord.

All this suggests that new factors may be developed in the course of time which may bring about something approaching a practical application of this kind of work. I believe the work, therefore, should be continued. On the other hand, from the point of view of practical neurology, what does this have to offer? My feeling is that the step between the demonstration of regenerating fibers in the spinal cord of dogs and cats and the restoration of function in a transected spinal cord in the human is a long step indeed. I hope that you will not consider me a pessimist if I say that, although I should like to feel that this work should be encouraged, neither you nor I will live to see this miracle.

DR. RALPH W. GERARD, Chicago (by invitation): Of course, I am pleased with the positive results of these expert neuroanatomists. My co-workers and I have made several attempts to solve the problem of central regeneration, originally on animals in utero, but later on animals up to 2 months old, which is a significant fraction of the rat's life span. I have tried to interest neurosurgeons in the possibility of this, but have succeeded only with Dr. Davidoff. As he indicated, his results were not encouraging; nevertheless, I remain optimistic.

Among our criteria of regeneration were these: An animal responded to application of petrolatum on the nose by sitting up on its hindlegs to use its front ones for wiping; it squealed when the tail was pinched; it gave vigorous movements of the hindquarters on stimulation of the cerebral peduncle. I remain satisfied that regeneration, functional as well as anatomic, did occur, and I have been happy that Dr. Freeman, in the last two years or so, has extended our relatively small series tenfold, with about the same proportion of successes.

Our own view has been that the main difficulty in central regeneration is a structural one, that growing fibers become entangled in the glial scar. A number of technics give hope of diminishing glial overgrowth, one of which was used in Dr. Windle's work. I am in no position to recommend to physicians how they should handle their patients, but it does seem to me that, since one is faced with absolute failure in doing nothing in many cases of spinal injury and since there is a possibility of doing something for the patient and, at the same time, of gaining further information as to ways of doing still more, the patients perhaps deserve an experimental therapeutic "benefit of the doubt."

News and Comment

NEW QUARTERLY

Psychological Book Previews is a new quarterly, starting publication in January 1951. It is intended to help psychologists keep up to date on new books in psychology and selected new books in anthropology, education, neurology, psychiatry, sociology and statistics. Each issue will have 40 to 50 descriptive summaries of books written by the authors before their books appear. A good description and a sample of the author's writing should be of help to prospective purchasers. For those interested in the opinion of reviewers, each issue will also contain a bibliography of over 300 critical book reviews. This journal will be edited by John W. French. The subscription price is $4.50 a year. Communications may be addressed to 31 Markham Road, Princeton, N. J.

FIRST WORLD PSYCHIATRIC CONGRESS

The International Congress of Psychiatry was held in Paris Sept. 18 to 27, 1950. Nearly 2,000 members, from 46 countries, attended. The proceedings of the Congress will be published in eight volumes in 1951. It was decided that all the countries in the world shall receive invitations to future congresses, which will be held every five years, and that the International Congress of Psychiatry of 1950 shall be called officially the First World Psychiatric Congress. The international committee has been appointed to choose the place and date of the next congress and to set up the statute of the new organization in conjunction with the UNESCO. Until the organizing committee of the next congress is appointed, correspondence should be addressed to Dr. Henri Ey, secretary of the World Psychiatric Congresses, I, Rue Cabanis, Paris XIVémè.

CORRECTION

The author of "Inhaltsberechnung der Rindensubstanz," (*Arch. f. Psychiat.* **54**:261, 1914) is R. Jaeger, not Yager, as in footnote 6 of the article entitled "Some Data Concerning the Growth and Development of the Cerebral Cortex in Man," by Oscar A. Turner, M.D., pubilshed in the September 1950 issue of the ARCHIVES, page 380.

SPECIAL NOTICE

For the general information of indexers, catalogers and library personnel with reference to the listing of the new title of this journal, we advise that the *Quarterly Cumulative Index Medicus* policy be followed. The *Quarterly Cumulative Index Medicus* with its volume 49 (January-June 1951) will list this journal under the new title, so that the letters A. M. A. will be included as an integral part of the title. For the completion of volume 48 (July-December 1950) the *Quarterly Cumulative Index Medicus* will continue to use the old title, without adding the designation A. M. A.

Book Reviews

Childhood and Society. By Erik H. Erikson. Price, $4. Pp. 397. W. W. Norton & Company, Inc., 101 5th Ave., New York 3, 1950.

In this important book, the author combines the insight of a psychoanalyst with the methods of an anthropologist. In this new approach, he succeeds to new depths of understanding in the relation between childhood and society. He deals with the social and psychological significance of childhood—the relations between child training and later cultural accomplishment, between early childhood fears and later social anxieties of the grown-up. The main chapters begin with descriptions of "specimen situations," data on which were gathered in the treatment of small children, in the rehabilitation of veterans of the war and in field work with American Indians. These observations are then applied in a fascinating analysis of modern ideologies affecting the youth of three industrial countries, with a special deep-going analysis of the ideology of the Hitler youth. The author gives new insight into the relation between the infantile and the mature, the modern and the archaic, in human motivation. The unusual long childhood dependency of man, while a prerequisite of human learning, leaves a residuum of emotional immaturity. If this childhood dependency is intensified in certain cultural settings and later exploited in adulthood, the resulting immaturity endangers man's work and further progress.

The application of psychoanalysis to the field of cultural anthropology has nowhere in literature found a more mature expression than in this book. Time and further research will show the fundamental significance of this work for the further progress in the development of psychoanalysis from an individual method of medical treatment into an instrument of social understanding.

Hypnodrama and Psychodrama. By J. L. Moreno, M.D., and James M. Enneis. Psychodrama Monograph 27. Price, $2.75. Pp. 56. Beacon House, Inc., 101 Park Ave., New York 17; Box 311, Beacon, N. Y., 1950.

The technic of hypnodrama is presented, and some theoretical considerations are added. Technical information is also given. Two verbatim protocols of hypnodramatic sessions are presented and discussed. The difference between hypnodrama and psychodrama is pointed out.

Sex in Psychoanalysis: Contributions to Psychoanalysis. By Sándor Ferenczi, M.D.; introduction by Clara Thompson, M.D.; preface by Ernest Jones. Price, $3.50. Pp. 338. Robert Brunner, 1212 Ave. of the Americas, New York 19, 1950.

The republication of this book reasserts Ferenczi's importance as a pioneer in psychoanalysis. The volume offers most important material and actually consists of reprints of Ferenczi's papers written from 1908 to 1914 and previously published under the title "Contribution to Psychoanalysis." It contains Ferenczi's most important work: "Stages in the Development of the Sense of Reality," which forms the first attempt at analytic ego psychology. Among the 15 papers are included Ferenczi's contributions to the understanding of symbolism, the interest in money, obscene words and the relation between homosexuality and paranoia. In the introduction, Ernest Jones states, "Apart from Freud, Ferenczi has perhaps made more original contributions to psychoanalysis then any other person." The analytic reader will again be impressed by the work of Ferenczi, about whom Freud once said, "He made us all his pupils."